ANNUAL REPORT
OF
PROGRAM ACTIVITIES
NATIONAL INSTITUTE OF DENTAL RESEARCH
Fiscal Year 1973

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service National Institutes of Health

ANNUAL REPORT

OF

PROGRAM ACTIVITIES

NATIONAL INSTITUTE OF DENTAL RESEARCH

Fiscal Year 1974

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NATIONAL INSTITUTE OF DENTAL RESEARCH

Part I---Office of the Director
Research Projects and Indexes

Part II--National Caries Program

Part III-Extramural Programs

Part IV--Intramural Research

Part V---Collaborative Research Projects

PART I

NATIONAL INSTITUTE OF DENTAL RESEARCH

ANNUAL REPORT

OFFICE OF THE DIRECTOR

RESEARCH PROJECTS AND INDEXES

July 1, 1973 - June 30, 1974

Compiled by

Dental Research Data Officer

National Institute of Dental Research

National Institutes of Health

Bethesda, Maryland

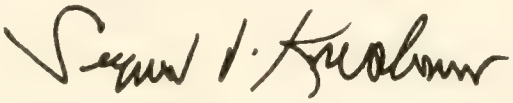
PREFACE

The NIDR Annual Report is intended to capture in printed form the essence of the Institute's total activities during the course of one fiscal year. The present format has evolved from our desire to make the Report more palatable to the reader, a better reference tool for its users, and less burdensome in preparation for its contributors.

A major change in compilation has been made in this issue to accommodate our several uses of the completed document. The Report for FY 1974 has been prepared in organizationally distinctive Parts to facilitate selective distribution to those who are concerned with or require as a working instrument less than the total publication. These are: Part I, Office of the Director, Research Projects and Indexes; Part II, National Caries Program; Part III, Extramural Programs; Part IV, Intramural Research; and Part V, Contracts.

For the third year, we have continued the practice of using a modified SSIE Notice of Research Project form (PHS 166) for the Individual Project Report. These are collected together as a section of Part I. This section, on blue paper, is accompanied by a number of indexes, for ease of retrieval and analysis, and a Classification Guide to Subjects and Categories.

We apologize in advance for any errors that may have escaped our attention and would appreciate your comments and suggestions so that we may continue to improve this document in the future.



Seymour J. Kreshover, D.D.S., M.D.
Director
NIDR

CONTENTS

PART I - OFFICE OF THE DIRECTOR	PAGE
Report of the Director	1
Office of Scientific and Health Reports	1
Planning, Analysis and Evaluation Activities	4
Financial Management Office	5
Personnel Office	5
Data Processing Systems and Analysis Section	6
Office of Collaborative Research	7
Dental Research Data Officer	8
PART I - RESEARCH PROJECTS AND INDEXES (Blue Section)	
Introduction to Indexes	iii
Indexes	
Research Projects by Cooperating Units	v
Research Projects by Investigator	vii
Research Projects by Number	xv
Research Projects by Subject Area	xix
Research Projects by Type of Research	xxxiii
Categories and Subjects	xxxv
Individual Project Reports	1
PART II - NATIONAL CARIES PROGRAM	
PART III - EXTRAMURAL PROGRAMS	
PART IV - INTRAMURAL RESEARCH	
PART V - CONTRACTS	

REPORT OF THE DIRECTOR

THE NATIONAL INSTITUTE OF DENTAL RESEARCH

July 1, 1973 - June 30, 1974

by

Seymour J. Kreshover

In the swirl of uncertainty over research priorities and support in the past year, a major stabilizing influence has been NIDR's long established pattern of continuous assessment and realignment of resources to carry out most effectively the Institute's mission. The Institute has what at once is a dual responsibility and opportunity: a unique concern with problems of the oral-facial complex and an involvement with basic research that transcends parochial boundaries and contributes knowledge to broader areas of human biology and disease.

The continuous assessment is made in concert with the Institute's senior scientific and administrative staff. It is noteworthy that the impetus for the reorganization this year came from the scientific leadership. As a result, a new Laboratory of Developmental Biology and Anomalies was established, and microbiological activities carried out in different components of the Institute were consolidated in the Laboratory of Microbiology and Immunology.

This continuing self-renewal has enabled NIDR to withstand the steady erosion in positions and to maintain a viable scientific base while at the same time making a meaningful contribution to the solution of this country's overwhelming oral health problems.

Office of Scientific and Health Reports

In mid-year the NIDR Information Office was redesignated the Office of Scientific and Health Reports to reflect more accurately the predominant character of its functions.

Celebration of NIDR's 25th anniversary in June 1973 has had a ripple effect which carried over into this fiscal year. For example, in the 1974 edition of the Encyclopedia Britannica Book of the Year, the section on "Dentistry" had the following lead paragraph:

"During 1973 the National Institute of Dental Research celebrated its 25th anniversary with a two-day special conference in Washington, D. C. The establishment of the NIDR in 1948 had climaxed an eight-year battle by the American Dental Association to obtain federal funds for dental research.

Since then, the NIDR budget had risen from an initial $237,000 to $40,333,000 in 1973. Although about 80% of NIDR's total appropriations were spent for extramural research and training activities, the intramural staff had played a pivotal role in advancing research into dental decay and periodontal (gum) disease."

The proceedings of the conference were published as a supplement to the October 1973 issue of the Journal of the American Dental Association and were distributed to all recipients of the journal. A review article, "NIDR at 25," which was included in the supplement has since been reprinted because it continues to be used extensively in response to requests for information on the Institute's activities.

In the absence of a clipping service and mass media reports, it is impossible to determine the full impact of communications efforts of the Office. For example, a press summary on grant-supported research prepared for release at the last IADR meeting was picked up by the AP wire service and prompted the local NBC television station to send a camera crew to the grantee's institution to film his work. The network released the footage on its feed, and other NBC affiliates pick it up. It came to our attention when someone saw it on a Baltimore channel, identified as research supported by the National Institute of Dental Research.

The Institute has been encouraged by the appropriations subcommittee of the House of Representatives, the National Advisory Dental Research Council, and the American Dental Association to keep dental practitioners more informed about research activities. In response, the Office of Scientific and Health Reports is enlarging its communications activities. One means being explored is the use of filmed (or videotaped) reports on current research activities of significance to the practitioner for showing at professional meetings and in dental schools. The pilot in this series will be a 10-minute film on the NIDR caries vaccine study. This film is in initial stages of preparation.

Another approach has been to prepare a brief review article on NIDR's contributions to the dental practitioner, entitled "Dental Research: Key to Prevention" for the Journal of the American Society for Preventive Dentistry.

A different professional audience will be reached by the article on "Fluoride - Cornerstone in the Fight Against Tooth Decay," prepared for a special dental issue of Pharmacy Times.

As part of the continuing effort to attract science-oriented students to dental research, the Office is cooperating with the American Dental Association in updating the booklet "Dental Science Projects for High School Science Students." In another approach to creating an awareness of dental research, a single-concept film on the scanning electron microscope for junior high schools was produced by the American Dental Association under grant support.

The film "Laboratory of the Body," produced in 1969 by the Association under grant support and the close supervision of the Office, continued to be shown widely to high school science students. Termination of the funding has resulted in the withdrawal of the film from the commercial distribution firm Modern Talking Picture Service. The last report from the firm showed that as of August 31, 1973, the cumulative number of persons who have seen the film since its introduction was 2.4 million, exclusive of dental students and the television audience. Prints of the film continue to be available to high school teachers and other interested groups through the American Dental Association and selected depository libraries.

In recognition of its broad range of activities in public and professional information, the Office was invited to participate in a briefing of a Congressional staff member exploring this area in anticipation of a comprehensive health insurance program.

Media contacts during the year on dental research or related subjects include the Reader's Digest, U. S. News and World Report, National Geographic, Wall Street Journal, Changing Times, Harper's Bazaar, McCall's, Woman's Day, Consumer Products, Family Health, Science Digest, Current Science, Medical Tribune, Chemical and Engineering News, Hospital World, United Press International, Medill News Service, Scripps-Howard, and Gannett Newspapers.

During the year 53,750 publications were distributed. The diversity of groups requesting materials is illustrated by the following: Wisconsin Department of Health and Social Services; Department of Human Resources, Dental Health Unit, Atlanta, Georgia; State Health Center, Department of Health, Commonwealth of Pennsylvania; Harvard University, Tooth Implant-Transplant Research Unit; Brookdale Dental Center of New York University, Preventive Dentistry and Community Health Department; Susan B. Anthony School for the Retarded, Jamaica, New York; Senior Citizens Program, Marion County Health Department, Salem, Oregon; and Dental Hygiene Department, Middlesex Community College, Massachusetts.

Exhibits were shown at 3 meetings: the American Dental Association, the National Association of Biology Teachers, and the National Science Teachers Association. Personnel from the Office of Scientific and Health Reports arranged for all exhibit showings and staffed the latter two meetings.

Substantial assistance was provided by staff in arranging for publication by the Government Printing Office of papers presented at the fourth symposium on oral sensation and perception.

A major expenditure of staff time is on internal reports and the requirements of specialized audiences. Such internal reports include weekly reports on research accomplishments, HEW quarterly reports, research and program highlights, opening statements to Congress, Presidential messages, and numerous other periodic and ad hoc reports.

In summary, the Office of Scientific and Health Reports this year answered 8,500 inquiries; distributed approximately 53,750 pieces of literature; exhibited at 3 meetings; prepared 102 press items, summaries, releases, and features, including a special article on "Tooth Decay, Silent Destroyer" for 139 house organs, 6 "Search for Health" columns, and a special feature on research on craniofacial anomalies; 12 radio spot announcements; arranged 3 radio/television interviews; wrote two articles for professional journals; and contributed material for a speech by the Secretary. The Office also arranged orientation programs and tours for approximately 43 visitors; processed 67 manuscripts and 53 abstracts as the NIDR clearance center; and prepared the NIDR component of the "NIH Annual Bibliography" and the "Professional Staff of NIDR" publication.

Planning, Analysis and Evaluation Activities

This activity serves as the focal point for planning, analysis, and evaluation in the Institute by (1) representing the Institute at NIH meetings on planning and evaluation; and (2) providing responses to the NIH Office of Program Planning and Evaluation on NIDR programs and activities.

Among its more important activities during the past year was coordination of the NIDR evaluation workshops and conferences which were supported by one percent set-aside funds. This effort involved the preparation of detailed guidelines for NIDR staff on procedures to be followed and the reports to be prepared as well as a comprehensive report to the NIH Associate Director for Program and Evaluation on NIDR's use of these special purpose funds in FY 1974 and as projected for FY 1975.

The activity also collaborated with the extramural scientist-administrators and intramural laboratory and branch chiefs in updating the annual comprehensive report, Research Plans of the National Institute of Dental Research; and was responsible for coordinating the work of the NIDR Ad Hoc Group on Program Balance. To date, this group, which is advisory to the Director, has developed a program planning strategy for the Institute, and presented the related data to the NADRC.

Another function was the preparation of a sample profile on a dental school and its parent university to serve as a prototype for determining how NIDR might better support and strengthen the science base of dental schools and how the dental schools can, in turn, best contribute to the NIDR's mission.

As a basis for the preparation, under contract, of two annual publications, National Institute of Dental Research Support Programs, and Dental Research in the US, Canada, and Great Britain, the Dental Research Data Officer provided guidance and data to the Science Information Exchange. The former publication was redesigned to include not only research and training grants and awards, but also research contracts, intramural projects, and research projects at the five NIDR Dental Research Institutes (Centers).

Another collaboration between extramural staff, the Director of Intramural Research, and the Data Processing Systems and Analysis Section resulted in the development of a subject classification which listed all research activities by salient characteristics, including FY 1974 dollar figures. This common classification allows for analyzing NIDR supported research in terms of diseases and disorders and such basic scientific areas as etiology, pathology, diagnosis and treatment, and prevention. The classification is also used to categorize the research projects reported in the two NIDR annual publications.

Financial Management Office

The Financial Management Office serves as the focal point within the Institute for budget data and related information. Its activities encompass several major areas: budget execution, payroll records, Office of Financial Management reports, special reports, monthly status reports, special management projects, and preparation and presentation of the annual budget. While this year's budget formulation and presentation activities were complicated by the release of impounded FY 1973 money, budget execution is a year-round activity, generating numerous plans and reports, from the apportionment plan to the special emphasis programs report.

During the past year, the Financial Management Office refined its use of Wylbur and Autotab systems (to produce status reports and projections), thereby increasing its efficiency. For example, several management reports were prepared for the Office of the Director on projected employment levels, travel reduction, and space allocations. The office also routinely prepared analytical projection of obligation patterns for the cost centers.

Other activities of this office included the issuance of monthly status reports on personnel and the rate of expenditures for program activities. These provide the budget office and administrative program directors with a reliable guide to assist in maximizing their personnel and financial resources. In addition, they provide the management decision centers (Executive Office and Personnel Office) with timely financial information to guide them in making decisions.

Finally, the Financial Management Office engaged in such diverse activities as the processing of some 500 payroll corrections and additions, preparation of reports on a variety of subjects, including average grade, on-duty personnel, grant forecasts, and special reports concerning the utilization of impounded funds.

Personnel Office

The Institute EEO Committee, recently reorganized to provide improved employee representation, met on a regular basis to discuss problems of concern and identify ways to advance both the Institute's Upward Mobility and EEO programs. Two new EEO Counselors/Council Members were appointed, one to represent employees located on the main NIH reservation and one to represent employees located in the Westwood Building.

In other activities, the Personnel Office continued its job-restructuring efforts and, in conjunction with the Institute's Animal Care Committee, implemented a training program which made possible the conversion and promotion of NIDR Animal Caretakers to Biological Laboratory Technicians (Animal). A Personnel Assistant position was also redesigned to provide a Personnel Management Specialist, thereby permitting a female employee to advance to professional status within the field of personnel management. A similar action was accomplished for an Administrative Technician whose job was restructured as an Administrative Officer.

Support for NIH-wide programs has continued, particularly in those areas that provided opportunities for the economically disadvantaged. Thus, the Institute has more than doubled its Stay-in-School assignments, increased the number of Summer Aids, provided support for a STRIDE intern in a training position within a laboratory, and continued its participation in the Federal Junior Fellowship Program. In addition, an Upward Mobility College Workshop for Supervisors was held during the reporting period.

Both on-the-job and outside training continued to be provided for employees, with emphasis on the broad categories of upward mobility and scientific and technical capability. Executive Development was also stressed with several executive seminars on decision analysis being held. A significant increase in the amount of course work in computer science has also been noted which should contribute greatly to better utilization of existing facilities by Institute staff. Efforts to increase the number of women in grades GS-11 and above have produced an increment of three; two by appointment and one by promotion. For the first time, a woman laboratory chief was promoted to the supergrade level.

Finally, during the reporting period, the NIDR Personnel Office became one of the first at NIH to fully participate in the Automated Retrieval of Manpower Statistics (ARMS) system. As a corollary, it was also a leader in developing a fully automated program for computing Civil Service employees' retirement annuities, one which is presently being considered for possible NIH-wide use.

Data Processing Systems & Analysis Section

The fundamental product of NIDR is information. As an information processor, the computer is being used to facilitate and extend the information processing capabilities of NIDR personnel. Accordingly, this Section is responsible for the design, development and implementation of data processing systems and procedures in support of NIDR program activities.

Organizationally and functionally, the Data Processing Section changed substantially during the past fiscal year. First, in order to better serve all components of the Institute, the Section was transferred to the Office of the Director (effective July 1973). Secondly, as a central service organization, the Section became involved in the provision of computer services to the three

mechanisms for performing or supporting research--intramural, contracts and grant activities. To accomplish these responsibilities, the Section was structured into two units, scientific and administrative. The scientific unit is involved primarily with intramural research efforts, while the administrative unit works mainly on grants and contracts data processing.

Scientific Unit

The laboratory automation system, now composed of two minicomputers sharing mass storage units, continues to provide increased service to the intramural laboratories. This project has been a collaborative effort with the Computer System Laboratory of DCRT. The system, consisting of Honeywell H316 and H516 computers, is engaged in the on-line data acquisition and real time processing of laboratory data. It is presently interfaced to the following set of instruments/experiments: (a) four scintillation counters; (b) one gas chromatograph; (c) one spectrophotometer; (d) one x-ray diffractometer; (e) one amino acid analyzer; (f) one fermentation control system; and (g) one neurophysiology stimulus-response instrument.

The system, which processes approximately one million data values each month, has provided significant research advantages for the Institute. However, in order to more fully acquaint NIDR personnel with the advantasges as well as the limitations of computers, a series of technical courses were offered by the Section during the past year.

Administrative Unit

The administrative unit designs and implements data systems for internal managerial and extramural information requirements. While its primary role is the production of reports on contracts and grants, it also serves the computer retrieval needs of the NIDR Dental Research Data Officer.

During the past year, a data base system was established for reporting on contracts and interagency agreements. Designed to supplement information needs not met by the DRG Impac system, this unit has the capability of tracking the progress of a contract or interagency agreement through various stages in the process from Request to Initiate a Contract (RIC) to Request for Proposal (RFP) to Award. Currently, the system provides four reports on a monthly basis: (1) Active Contracts; (2) Contract Commitments; (3) a summary of Contract Commitment; and (4) an accounting of Contract Balance.

Office of Collaborative Research

During the fiscal year 1974, this office continued to execute the initial review of contracts and interagency agreements as detailed in last year's Annual Report. Twenty-three requests for proposals were received, approved and processed. Two of these were for sole source procurements; the others resulted in the receipt of from two to twenty-four proposals each. These proposals have all been reviewed or are being reviewed now. Two RFPs were cancelled because the proposals received were not of sufficiently high technical merit to warrant funding.

Two bona fide unsolicited proposals were received, both from industrial concerns. Both were rejected by the National Caries Program for lack of high program relevance.

The measures adopted by the Office last year to assure the timely receipt of progress reports have been successful. Similarly, the NIDR procedure for releasing RFPs earlier in the year greatly reduced the fourth quarter review and approval overload.

Presently the Institute has 55 active research and development contracts, as well as 10 interagency agreements. It is estimated that there will be 73 active contracts and 12 interagency agreements by June 30, 1974.

Dental Research Data Officer

The principal function of this office is to provide data or to answer questions concerning all aspects of dental research. The quality of the responses offered may vary with the degree to which the Institute is involved in a particular subject area, but the boundaries of our interest in matters related to dental research are unlimited. Basically, our operation resembles the classic specialized information center, and while we are primarily concerned with serving the needs of the Institute, we attempt to serve the needs of others as well.

During the last year we averaged over one recordable request per week. The majority of these requests were concerned with the details of NIDR research activities--the numbers and kinds of research supported; the amount of support for specific periods of time; and the subject areas involved. Though fewer in number, a variety of more distantly related topics were addressed by this office as well. Examples of the latter include: a list of female faculty members in dental schools; international expenditures for dental care; Federal support of research in pain; teratology research; research support of the neurosciences; health sciences education support in Latin America; potential research and education manpower losses; number and distribution of dental specialists; and dental diseases in tropical climates.

As a parallel activity to these ad hoc requests, a large number occur regularly, year after year. At the present, these recurring requests include the: National Science Foundation Annual Report of Scientific and Technical Information Activities; Minority Grants Program Data; Nutrition Research; Catalog of Federal Domestic Assistance; Federal Inventory of Population Research; National Heart, Blood Vessel, Lung, and Blood Program; Water Resources Research Catalog; Research on Children's Diseases; Indian Health; Oceanography and Marine Biology; and Support of International Activities.

An analysis of our records shows that 58 percent of the requests come from within NIDR, 29 percent from other areas of the Federal Government, and 14 percent from the non-Federal sector. Similarly, the information sources that we used for compiling these responses were distributed as follows: 65 percent from NIDR, 22 percent from other areas of the

Federal government, and 14 percent from non-Federal sources. It is of some significance that we must depend on areas other than NIDR for much of the information processed by this office. For this reason, a close personal relationship is established and maintained with key personnel in the many data gathering activities of related Government Agencies and professional organizations.

The mechanisms employed for our functional operation are varied and range from manual searches to more sophisticated computerized and microrecord techniques. We continue to use the Division of Research Grants data base through the newly organized NIDR Data Processing Systems and Analysis for large, comprehensive, periodic, historical or complex reports but can, when necessary, interrogate the data base directly by means of our own terminal.

The broader dental research data base, which consists of ongoing research at the Smithsonian Science Information Exchange; the collection of Government sponsored research reports at the National Technical Information Service; and the entire range of published research material services provided by the National Library of Medicine, is regarded by this office as typical of the external resources available and among those most frequently used.

A number of manual record systems within the Office of the Dental Research Data Officer have been established or streamlined to expedite the delivery of routine responses. These have proven to be particularly useful in our operation which is limited in personnel and time.

Much of the data is so essential to such a large number of users that it is compiled and published on an annual basis. These documents serve to answer most of the questions concerning grants, awards, contracts and intramural activities and become a permanent record of such matters for the future. Specific titles include: NIDR Grants and Awards, Trainees and Fellows Supported by the NIDR, Dental Research in the United States, Canada, and Great Britain, and the NIDR Annual Report.

Like others in the Institute, the Dental Research Data Officer is frequently involved in committee work or consultation activities. One of the most time-consuming projects in this fiscal year was the NIDR/EP Manpower Utilization Study. In addition to the manpower study, assistance was given to two other major Extramural Program activities--the development of an Operations Manual for EP Scientist Administrators and a Dental Study Section Committee. Consultant activities outside of the Institute included an appointment by the American Dental Association Council on Dental Research for Logistics and Research Manpower; participation in discussions by the American Association of Dental Schools' Council of Sections Ad hoc Committee on Interdisciplinary Guidelines for Teaching Dental Students; input to planning a Learning Resource Building for Howard University; and review of a grant proposal to the American Fund for Dental Health.

The NCI/NIDR Followup Survey of Graduate Trainees and Postdoctoral Fellows (Contract NIH-NCI-0-72-3891) was successfully completed in August. Cooperation was excellent, response rate high, and valuable data were collected for our permanent records. Results weighed heavily against the comments of critics who claimed that there was an oversupply of scientists and that it was unnecessary for the Federal Government to support graduate education in selected fields of biomedical research. Fewer than one percent of our trainees and fellows were unemployed and over half of the respondents said they could not have entered their field of biomedical research without Federal support for their education and training.

A similar study began this year to determine the best means of communicating with dental scientists. In order to expedite the progress of oral health research, it is necessary to have a working knowledge of the various information channels now operating in the dental research community. A contractor will survey NIDR-supported research investigators--a sample population that represents about 20 percent of the known active dental researchers in this country. Hopefully, the results will be used to inform potential investigators of research needs identified by NIDR and support opportunities available--and further, that the time lag between discovery and utilization can be significantly shortened.

The year has not been without its disappointments and frustrations, but none have been insurmountable. The future calls for a sharper focus of responsibility and operational reinforcement by better organization of inhouse resources and more extensive utilization of outside strengths. The brief list of accomplishments recorded in the previous paragraphs and the satisfaction derived therefrom have been rewarding and inspiring.

NIDR ANNUAL REPORT

RESEARCH PROJECTS AND INDEXES

INTRODUCTION

The National Institute of Dental Research has modified the SSIE Notice of Research Project form (PHS 166) for use as an Individual Project Report. These reports are compiled, classified, and printed along with a number of indexes on blue paper to form a separate section of Part I of the NIDR Annual Report for FY 1974.

Project reports are classified in several ways. The investigators start by underlining the terms or concepts in the title and summary of their reports that they feel are most significant. The Director of Intramural Research assigns an NIDR classification code number to the project for planning and budgeting purposes. Finally, the Dental Research Data Officer, from the information thus obtained and his own knowledge of the data requests levied on the Institute may assign other keywords to the project. When possible, keywords are made to conform to those in the National Library of Medicine's Medical Subject Headings (MeSH). However, other terms, because they are new or unique to dental research may also be used. For a complete list of the subjects used in the Annual Report, see Subjects and Categories.

For convenience of reference and because some terms have dual meanings (e.g. "biochemistry" is a Field of Science and a Technic), six categories of subjects have been identified and coded. They are:

(A) Diseases and Disorders
(B) Fields of Science and Related Subjects
(C) Technics and Equipment
(D) Biomaterials, Chemicals, and Drugs
(E) Anatomical Terms
(F) Organisms and Named Groups of People

NIDR investigators are encouraged to refer to these subjects and categories or to MeSH in developing titles and summaries for new projects.

Project numbers, which have been a source of confusion in past years, have been revised again this year. Our goal is to have research projects carry the same identifying number throughout their lifetime. Earlier attempts were thwarted by organizational changes. The present system is based on beginning date and last name of principal investigator.

The indexes for this issue of the Annual Report were prepared with the assistance of the Data Processing Systems and Analysis Section.

NIDR ANNUAL REPORT - FY 74

INDEX

RESEARCH PROJECTS BY COOPERATING UNITS

COOPERATING UNITS	PAGE
AMERICAN DENTAL ASSOCIATION	38
AMERICAN TYPE CULTURE COLLECTION, BETHESDA, MD	23
AMERICAN TYPE CULTURE COLLECTION, BETHESDA,MD	66
C AND Y PROJECT NO. 660, ROBSTOWN, TEXAS	65
CENTER FOR DISEASE CONTROL, ATLANTA, GEORGIA	66
CLINICAL CENTER, NIH	77
CLINICAL CENTER, NIH	88
CLINICAL CENTER, NIH	120
D. C. GENERAL HOSPITAL	126
DCRT, NIH	45
DCRT, NIH	30
DENTAL DIVISION MONTANA STATE HEALTH DEPT	37
DEPT. OF THE ARMY, DENTAL CO. FORT KNOX	84
DIV. OF RES. SERVICES, MAPB	50
DUKE UNIVERSITY , DURHAM, NORTH CAROLINA	93
ENVIRONMENTAL PROTECTION AGENCY	29
FOGARTY INTERNATIONAL CENTER	81
FORSYTH DENTAL CENTER, BOSTON, MASSACHUSETTS	124
FORSYTH DENTAL CENTER, BOSTON, MASSACHUSETTS	45
GEORGE WASHINGTON UNIVERSITY	16
GEORGETOWN UNIVERSITY, WASHINGTON, D. C	45
GEORGETOWN UNIVERSITY, WASHINGTON, D. C	17
GEORGETOWN UNIVERSITY, WASHINGTON, D. C	17
HAZELTON LABORATORIES	83
HERSHEY MEDICAL CENTER, HERSHEY, PENNSYLVANIA	64
HOSPITAL FOR SICK CHILDREN, TORONTO	38
JOHNS HOPKINS HOSPITAL, BALTIMORE, MD	9
KENDALL COMPANY, BARRINGTON, ILLINOIS	40
LANCASTER CLEFT PALATE CLINIC, LANCASTER, PA	5
LITTON BIONETICS, BETHESDA, MARYLAND 20014	35

COOPERATING UNITS PAGE

LITTON BIONETICS, BETHESDA, MARYLAND 20014.....129
MONTREAL CHILDREN'S HOSPITAL, MONTREAL,CANADA..... 78
NATIONAL BUREAU OF STANDARDS..... 2
NATIONAL CANCER INSTITUTE.....123
NATIONAL CANCER INSTITUTE..... 42
NATIONAL CANCER INSTITUTE..... 11
NATIONAL HEART AND LUNG INSTITUTE..... 19
NATIONAL INSTITUTE OF CHILD HEALTH AND DEVELOPMENT..... 81
NATIONAL NAVAL MEDICAL CENTER.....126
NELSON COUNTY PUBLIC SCHOOL SYSTEM..... 72
NEW YORK MEDICAL COLLEGE, NEW YORK, NY..... 76
NIAMD, NIH..... 28
NIAMD, NIH..... 19
NIAMD, NIH..... 36
NORTH CAROLINA STATE BOARD OF HEALTH.....115
NORTH CAROLINA STATE BOARD OF HEALTH..... 29
NORTH CAROLINA STATE BOARD OF HEALTH..... 73
NORTH CAROLINA STATE BOARD OF HEALTH..... 32
NORTHWESTERN UNIVERSITY, BOSTON, MASS.....106
OXFORD UNIVERSITY..... 2
PUBLIC SCHOOLS OF WAYNE COUNTY, N C..... 32
ROBERT B. BRIGHAM HOSPITAL, BOSTON, MASS..... 77
ROYAL DENTAL COLLEGE, COPENHAGEN, DENMARK..... 15
STATE UNIVERSITY OF NEW YORK..... 22
TATA INSTITUTE OF RESEARCH, BOMBAY INDIA..... 21
TEMPLE UNIVERSITY, PHILA. PA..... 62
ROYAL DENTAL COLLEGE, COPENHAGEN, DENMARK..... 21
UNIVERSITY OF CONNECTICUT HEALTH CENTER..... 33
UNIVERSITY OF CONNECTICUT HEALTH CENTER.....103
UNIVERSITY OF DETROIT.....115
UNIVERSITY OF HAWAII..... 14
UNIVERSITY OF ILLINOIS..... 50
UNIVERSITY OF MARYLAND.....119
UNIVERSITY OF MARYLAND..... 23
UNIVERSITY OF MASSACHUSETTS..... 38
UNIVERSITY OF NORTH CAROLINA..... 38
UNIVERSITY OF QUEENSLAND, BRISBANE, AUSTRALIA..... 45
UNIVERSITY OF ROCHESTER, ROCHESTER, N. Y..... 47
UNIVERSITY OF ROCHESTER, ROCHESTER, N. Y..... 63
VA HOSPITAL, HINES, ILLINOIS..... 17
VANDERBILT UNIVERSITY, NASHVILLE, TENNESSEE..... 95
VANDERBILT UNIVERSITY, NASHVILLE, TENN.....107
VETERINARY RESOURCES BR., NIH.....103
VIRGINIA DEPARTMENT OF HEALTH..... 72
WALTER REED ARMY MEDICAL CENTER..... 47
WASHINGTON UNIVERSITY, ST. LOUIS, MO..... 75

TOTAL NUMBER OF COOPERATIVE PROJECTS 76

TOTAL NUMBER OF COOPERATIVE UNITS 57

NIDR ANNUAL REPORT - FY 74

INDEX

RESEARCH PROJECTS BY INVESTIGATOR

INVESTIGATOR	PAGE
*ALTMAN, LEONARD C	42
ALTMAN, LEONARD C	35
*AMSBAUGH, SUZANNE	79
*ARCHARD, HOWELL O	19
*ARCHARD, HOWELL O	11
BEAMAN, ALFRED	52
BECHTOLD, JUDITH A	63
BECK, WILLIAM D	130
BECK, WILLIAM D	121
*BEITEL, RALPH E	49
BENEDICT, FRANCES	124
BENVENISTE, KATHY	25
BHAKDINARONK, ANONKNART	38
BILLUPS, LLOYD	85
*BINCK, JOAN M	80
BINCK, JOAN M	64
BINGLE, GLENN J	5
BINGLE, GLENN J	4
BLADEN, HOWARD A	33
*BLADEN, HOWARD A	69
*BOSMA, JAMES F	81
*BOSMA, JAMES F	50
*BOUCHER, D. WARK	82
*BOWEN, WILLIAM H	83
BOYD, DALE	83
BROWN, ELINOR	86
BROWN, FREDERICK J	49
*BROWN, FREDERICK J	31

INVESTIGATOR PAGE

*BROWN, KENNETH S..... 24
BROWN, KENNETH S..... 38
*BROWN, KENNETH S..... 3
BROWN, KENNETH S.....109
BROWN, TECOLIA I..... 82
BRUNELLE, JANET ANN..... 99
*BRUNELLE, JANET ANN..... 84
BRUNELLE, JANET ANN..... 66
BRUNELLE, JANET ANN.....104
*BURNS, WILLIAM H..... 85
BYERS, PETER..... 9
CHANDRAKASAN, G..... 10
CHASE, NINA..... 22
CHASSY, BRUCE M..... 44
*CHASSY, BRUCE M..... 43
CHITE, ANTHONY F.....105
CHITE, ANTHONY F.....106
CHUNG, C. S..... 14
*CHUNG, S. I..... 51
CHUSED, THOMAS M..... 53
*CHUSED, THOMAS M..... 87
*CHUSED, THOMAS M..... 86
CHUSED, THOMAS M..... 96
CHUSID, MICHAEL J..... 91
*CIARDI, JOSEPH E..... 52
COLWELL, R. R..... 45
*COOPER, HERBERT L..... 8
COOPER, HERBERT L..... 55
*CUMMINGS, NORMAN A..... 53
*CUMMINGS, NORMAN A..... 27
*CUMMINGS, NORMAN A..... 26
CUMMINGS, NORMAN A..... 93
*CUMMINGS, NORMAN A..... 88
DE STOPPELAAR, J. D..... 69
DELEON, HECTOR A..... 44

INVESTIGATOR PAGE

*DONKERSLOOT, JACOB A..... 44
DOUGHERTY, SUANNE F..... 35
DOUGHERTY, SUANNE F..... 47
DRISCOLL, WILLIAM S..... 72
*DRISCOLL, WILLIAM S..... 32
DROBIS, JEFFERY.....116
*DROBIS, JEFFERY..... 89
*DUBNER, RONALD..... 18
DUBNER, RONALD..... 64
DUBNER, RONALD..... 80
DUBNER, RONALD..... 49
DUBNER, RONALD..... 41
DUTTON, DAVID A.....130
DUTTON, DAVID A.....130
EANES, EDWARD D..... 76
*EANES, EDWARD D..... 70
*EANES, EDWARD D..... 90
*EANES, EDWARD D..... 36
ELLIS, ROYD.....122
ELLIS, ROYD.....123
EVANS, H. J..... 10
FISCHLER, CYNTHIA.....116
FOLIO, JOHN.....130
FOLK, J. E..... 51
*FOLK, J. E..... 1
*FOWLER, BRUCE O..... 12
*FRED, STEPHEN R..... 91
FRED, STEPHEN R.....130
FRIDBERG, ANDREW P..... 61
*FUJIBAYASHI, TAKASHI..... 92
FUJIBAYASHI, TAKASHI..... 96
GEIS, SHIRLEY..... 96
*GIBSON, WILLIAM A..... 17
*GOBEL, STEPHEN..... 20
GOBEL, STEPHEN..... 64
GOBEL, STEPHEN..... 80
GRAYKOWSKI, EDWARD A..... 88
*GRAYKOWSKI, EDWARD A..... 93
GRAYKOWSKI, EDWARD A..... 98
GRAYKOWSKI, EDWARD A..... 96
GRAYKOWSKI, EDWARD A..... 27
GREENMAN, VIVIAN.....114
GROSS, N. A..... 1
*HAGEAGE, GEORGE J., JR..... 33
HAGEAGE, GEORGE J., JR.....111
HAGEAGE, GEORGE J., JR..... 98
HAGEAGE, GEORGE J., JR..... 52
HAGEAGE, GEORGE J., JR.....103

INVESTIGATOR PAGE

*HAMNER, JAMES E. III..... 21
*HAND, ARTHUR R..... 28
*HAND, ARTHUR R..... 71
HASSELL, JOHN R..... 71
HASSELL, JOHN R.....108
HASSELL, JOHN R..... 59
HASSELL, JOHN R.....107
*HASSELL, JOHN R..... 54
HASSELL, JOHN R..... 38
*HASSELL, JOHN R..... 95
HAYASHI, KOZABURO.....122
HAYASHI, KOZABURO.....112
*HAYASHI, KOZABURO..... 94
HAYASHI, KOZABURO..... 96
*HEIFETZ, STANLEY B..... 29
HEIFETZ, STANLEY B..... 32
HEIFETZ, STANLEY B..... 37
HEIFETZ, STANLEY B..... 72
*HOOK, WILLIAM A..... 34
*HOOKS, JOHN J..... 96
HOOKS, JOHN J..... 93
HOOKS, JOHN J..... 92
*HOROWITZ, HERSCHEL S..... 37
HOROWITZ, HERSCHEL S..... 32
HOROWITZ, HERSCHEL S..... 29
*HOROWITZ, HERSCHEL S..... 72
IBA, BARBARA Y..... 5
IBA, BARBARA Y..... 4
IVERSON, G. MICHAEL.....110
*IVERSON, G. MICHAEL..... 97
IVERSON, G. MICHAEL..... 48
*JAKOBY, S..... 55
*JOHNSTON, MALCOLM C..... 38
JOHNSTON, MALCOLM C..... 5
JOHNSTON, MALCOLM C..... 24
JOLY, OLGA G.....115
*JOLY, OLGA G..... 73
KENNEDY, JOHN B..... 97
KENNEDY, JOHN B..... 48
KENNEDY, JOHN B..... 42
KERZA-KWIATECKI, MARGARET..... 97
*KEYES, PAUL H..... 98
KEYES, PAUL H.....111
KEYES, PAUL H..... 33
KEYES, PAUL H.....120
KEYES, PAUL H.....129

INVESTIGATOR PAGE

KING, C. T. G..... 54
KING, C. T. G.....107
KING, C. T. G..... 16
KING, C. T. G.....101
KING, C. T. G..... 59
KING, C. T. G.....102
*KING, C. T. G..... 74
*KING, C. T. G..... 13
KLINE, KIMBERLY..... 22
KORTS, DAVID C..... 32
*KORTS, DAVID C.....100
*KORTS, DAVID C..... 99
KRICHEVSKY, MICAH I..... 56
KRICHEVSKY, MICAH I..... 43
*KRICHEVSKY, MICAH I..... 45
KRICHEVSKY, MICAH I..... 23
KURISU, KOJIRO..... 5
*KUSHNER, DAVID C.....101
*KUSHNER, DAVID C.....102
LAPAGE, S. P..... 45
LARSON, MARY ALICE..... 38
*LARSON, RACHEL H..... 40
LARSON, RACHEL H.....106
LARSON, RACHEL H..... 15
*LARSON, RACHEL H.....103
LARSON, RACHEL H..... 79
LAW, FRANK E..... 29
LEVIN, DAVID P.....116
LEVIN, DAVID P..... 89
LEYSHON, WEBSTER C..... 3
LEYSHON, WEBSTER C..... 24
LITTLE, WAYNE.....124
*LONDON, JACK..... 22
*LOVE, LESLIE L..... 56
LUSTBERG, T..... 9
*MARTHALER, THOMAS.....104
*MARTIN, GEORGE R..... 9
MARTIN, GEORGE R.....109
*MARYANSKI, JAMES H..... 57
*MEDLIN, TERRY P..... 58
*MEDLIN, TERRY P..... 30
MERGENHAGEN, STEPHAN E..... 62
MERGENHAGEN, STEPHAN E..... 63
MERGENHAGEN, STEPHAN E..... 47

INVESTIGATOR PAGE

MEYERS, RHEA..... 72
MILLER, CAROL.....115
MILLER, CAROL.....114
*MIRTH, DALE B.....106
*MIRTH, DALE B.....105
MURAYAMA, DIANE R..... 50
NICHOLLS, A. C..... 10
*NISWANDER, JERRY D..... 14
*NISWANDER, JERRY D..... 4
*NISWANDER, JERRY D..... 5
NORTON, L..... 45
NOTKINS, ABNER LOUIS.....113
NOTKINS, ABNER LOUIS..... 96
NOTKINS, ABNER LOUIS.....125
NOTKINS, ABNER LOUIS.....112
NOTKINS, ABNER LOUIS..... 92
NOTKINS, ABNER LOUIS..... 94
NOTKINS, ABNER LOUIS..... 82
NOTKINS, ABNER LOUIS..... 85
NYLEN, MARIE U..... 75
*NYLEN, MARIE U..... 15
*NYLEN, MARIE U.....107
OPPENHEIM, JOOST J.....128
OPPENHEIM, JOOST J..... 60
*OPPENHEIM, JOOST J..... 35
OPPENHEIM, JOOST J..... 97
*OPPENHEIM, JOOST J..... 47
OPPENHEIM, JOOST J..... 48
OPPENHEIN, JOOST J.....129
ORKIN, R..... 9
PALUMBO, EMILY VICTORIA..... 43
PALUMBO, M. P..... 7
PHILLIPS, JEAN K..... 63
*PIEZ, K. A..... 10
*PIEZ, K. A..... 2
POULSEN, SVEN.....100
POULSEN, SVEN..... 37
PRATT, ROBERT M., JR..... 38
*PRATT, ROBERT M., JR.....108
*PRATT, ROBERT M., JR..... 59
*PRATT, ROBERT M., JR.....109
PRATT, ROBERT M., JR..... 95
PRICE, RICHARD.....125

INVESTIGATOR PAGE

*RADENZ, WILLIAM..... 60
*RADENZ, WILLIAM.....110
REYNOLDS, GEORGE R., JR..... 99
REYNOLDS, GEORGE R., JR.....104
ROBINSON, MERLE S..... 30
*ROBRISH, STANLEY A.....111
ROBRISH, STANLEY A..... 98
ROBRISH, STANLEY A.....120
ROGOSA, MORRISON..... 45
*ROGOSA, MORRISON..... 23
ROSENSTREICH, DAVID..... 47
ROSENSTREICH, DAVID..... 35
*ROSENSTREICH, DAVID..... 61
*ROSENSTREICH, DAVID..... 62
ROSENSTREICH, DAVID.....128
*ROSENTHAL, JOEL D.....112
*ROSS, MICHAEL E.....113
ROWE, D..... 9
*SANDBERG, ANN L..... 63
*SCHIFFMANN, ELLIOTT..... 6
SENNING, RICKLEY S..... 99
SENNING, RICKLEY S..... 88
*SHERN, ROALD J.....115
*SHERN, ROALD J.....114
SIRAGANIAN, REUBEN P..... 34
SIRAGANIAN, REUBEN P..... 89
*SIRAGANIAN, REUBEN P.....116
SKERMAN, V. B. D..... 45
SMITH, B..... 9
SOCRANSKY, S. S..... 45
STARKMAN, SIDNEY..... 41
*STARKMAN, SIDNEY..... 64
*STERN, R..... 25
*STILES, HORACE MCELREATH.....118
*STILES, HORACE MCELREATH..... 65
STILES, HORACE MCELREATH.....103
*STILES, HORACE MCELREATH.....117
*STILES, HORACE MCELREATH.....119
SUMINO, RHYUJI..... 80
SUMINO, RHYUJI..... 64
*SUMINO, RHYUJI..... 41
*SWEET, JAMES B.....120
SWEET, JAMES B.....130
SWEET, JAMES B.....129
SWEET, JAMES B..... 91
*SWEET, JAMES B.....121

INVESTIGATOR PAGE

TARPLEY, THOMAS M, JR..... 53
*TARPLEY, THOMAS M. JR.....122
*TARPLEY, THOMAS M. JR.....123
*TERMINE, JOHN D..... 76
*TERMINE, JOHN D..... 75
THACH, BRADLEY T.....126
THOMSON, L. ARIEL..... 33
*THOMSON, L. ARIEL.....124
*THOMSON, L. ARIEL..... 66
VAN BOXEL, J..... 61
WAHL, L..... 9
WAHL, SHARON M..... 97
*WAHL, SHARON M..... 48
WAHL, SHARON M..... 47
*WALZ, M. ANTIONETTE.....125
WASHINGTON, JULIAN H..... 34
WEBBER, RICHARD L.....130
WEBBER, RICHARD L..... 98
*WEBBER, RICHARD L..... 68
*WEBBER, RICHARD L..... 67
WEBBER, RICHARD L.....111
WEEDON, LYNDA L..... 47
WEEDON, LYNDA L..... 62
*WEIFFENBACH, JAMES M.....126
WEIFFENBACH, JAMES M..... 81
WESTERGAARD, JYTTE..... 15
*WILK, ANN L..... 16
*WILK, ANN L.....127
WILSON, JOHN J..... 30
*WILTON, MARK.....128
WITTENBERGER, CHARLES L..... 57
WITTENBERGER, CHARLES L..... 52
*WITTENBERGER, CHARLES L..... 7
WOHLENBERG, CHARLES R.....125
WOLF, ROBERT O.....113
*WOLF, ROBERT O..... 78
*WOLF, ROBERT O..... 77
WRIGHT, WILLIAM E..... 98
*WRIGHT, WILLIAM E.....129
*WRIGHT, WILLIAM E.....130

TOTAL NUMBER OF INVESTIGATORS 149

TOTAL NUMBER OF PRINCIPAL INVESTIGATORS 89

* PRINCIPAL INVESTIGATOR

NIDR ANNUAL REPORT - FY 74

INDEX

RESEARCH PROJECTS BY NUMBER

PREVIOUS NUMBER	CURRENT NUMBER	PAGE
LBC302B52	52B-001	1
LBC101B52	52B-002	2
HGB001A54	54A-003	3
HGB007A58	58A-004	4
HGB009A58	58A-005	5
LBC202B61	61B-006	6
LMI013B61	61B-007	7
LBC401B62	62B-008	8
LBC201B62	62B-009	9
LBC102B62	62B-010	10
EPB003A63	63A-011	11
LBS206B63	63B-012	12
LBS401B63	63A-013	13
HGB008A63	63A-014	14
LBS101B63	63B-015	15
LBS431B63	63A-016	16
EPB001B64	64B-017	17
DIR203B65	65B-018	18
EPB004A66	66A-019	19
DIR201B66	66B-020	20
EPB006C66	66C-021	21
LMI010B66	66B-022	22
LMI014B66	66B-023	23
HGB003B67	67B-024	24
LBC402B67	67B-025	25
OMS008C68	68C-026	26
OMS009C68	68C-027	27
LBS111B68	68B-028	28

PREVIOUS NUMBER	CURRENT NUMBER	PAGE
CPR002A68	68C-029	29
DIR001A68	68A-030	30
DIR204A69	69A-031	31
CPR003A69	69A-032	32
LBS320B69	69B-033	33
LMI003B69	69B-034	34
LMI004B69	69B-035	35
LBS202B70	70B-036	36
CPR001A70	70C-037	37
HGB004B70	70B-038	38
CPR022B70	70A-039	40
DIR202B70	70B-040	41
LMI008B71	71B-041	42
DIR106B71	71B-042	43
DIR105B71	71B-043	44
DIR108A71	71A-044	45
LMI002C71	71C-045	47
LMI008B71	71B-046	48
DIR206A72	72A-047	49
OPD003C72	72B-048	50
LBC301B72	72B-049	51
LMI012B72	72B-050	52
OMS008C72	72C-051	53
LBS421B72	72B-052	54
LBC404B72	72B-053	55
DIR102B72	72B-054	56
LMI019B72	72B-055	57
DIR002A72	72A-056	58
LBS421B72	72B-057	59
LMI022B72	72B-058	60
LMI023B72	72B-059	61
LMI024B72	72B-060	62
LMI021B72	72B-061	63
DIR205B72	72B-062	64
CPR008B72	72B-063	65
CPR009B72	72A-064	66
OMS016C72	72C-065	67
OMS017C72	72C-066	68
LBS301B73	63B-067	69
LBS201B73	73B-068	70
LBS121B73	73B-069	71
CPR026C73	73C-070	72
CPR027C73	73C-071	73
LBS441B73	73A-072	74
LBS204B73	73B-073	75

PREVIOUS NUMBER	CURRENT NUMBER	PAGE
LBS205B73	73B-074	76
OMS021C73	73C-075	77
OMS022C73	73C-076	78
NONE	74A-077	79
NONE	74B-078	80
NONE	74A-079	81
NONE	74B-080	82
NONE	74A-081	83
NONE	74A-082	84
NONE	74B-083	85
NONE	74B-084	86
NONE	74C-085	87
NONE	74C-086	88
NONE	74B-087	89
NONE	74B-088	90
NONE	74C-089	91
NONE	74B-090	92
NONE	74C-091	93
NONE	74B-092	94
NONE	74A-093	95
NONE	74B-094	96
NONE	74B-095	97
NONE	74C-096	98
NONE	74A-097	99
NONE	74A-098	100
NONE	74A-099	101
NONE	74A-100	102
NONE	74A-101	103
NONE	74A-102	104
NONE	74A-103	105
NONE	74A-104	106
NONE	74B-105	107
NONE	74B-106	108
NONE	74B-107	109
NONE	74B-108	110
NONE	74C-109	111
NONE	74B-110	112
NONE	74B-111	113
NONE	74C-112	114
NONE	74C-113	115
NONE	74B-114	116
NONE	74A-115	117
NONE	74A-116	118
NONE	74A-117	119
NONE	74C-118	120

NONE	.....	74C-119	121
NONE	.....	74C-120	122
NONE	.....	74C-121	123
NONE	.....	74A-122	124
NONE	.....	74B-123	125
NONE	.....	74B-124	126
NONE	.....	74A-125	127
NONE	.....	74B-126	128
NONE	.....	74C-127	129
NONE	.....	74C-128	130

TOTAL NUMBER OF RESEARCH PROJECTS 128

NIDR ANNUAL REPORT - FY 74

INDEX

RESEARCH PROJECTS BY SUBJECT AREA

SUBJECT AREA		PAGE
ACTINOBOLIN	D	117
ACTINOMYCES	F	69
ACTINOMYCES	F	103
ACTINOMYCES	F	7
ADENOSINE MONOPHOSPHATE	D	109
ADHESIVES SEALANTS	D	37
AMINO ACID SEQUENCE	B	10
AMYLASE	D	78
ANATOMY	B	50
ANTI-INFECTIVE AGENTS	D	120
ANTIBODIES	D	97
ANTIBODIES	D	112
ANTIBODIES	D	122
ANTIBODY FORMATION	B	116
ANTIBODY FORMATION	B	26
ANTICARIES AGENTS	D	105
ANTICARIES AGENTS	D	106
ANTICARIES AGENTS	D	114
ANTIGENS	D	112
ANTIGENS	D	128
ANTIGENS	D	53
ANTIPLAQUE AGENTS	D	106
ANTIPLAQUE AGENTS	D	115
ANTIPLAQUE AGENTS	D	105
APATITES	D	90
APATITES	D	70
APATITES	D	12

SUBJECT AREA		PAGE
APHTHOUS STOMATITIS	A	26
APHTHOUS STOMATITIS	A	27
ASCARIS	F	10
AUTOMATION	C	30
AUTOMATION	C	58
AUTORADIOGRAPHY	C	108
BACTEREMIA	A	120
BACTEREMIA	A	91
BACTERIA	F	111
BACTERIA	F	124
BACTERIA	F	83
BACTERIA	F	103
BACTERIA	F	98
BACTERIA	F	79
BACTERIA	F	57
BACTERIA	F	69
BACTERIA	F	66
BACTERIA	F	65
BACTERIA	F	7
BACTERIA	F	6
BACTERIA	F	23
BACTERIA	F	22
BACTERIA	F	33
BACTERIA	F	52
BACTERIA	F	45
BACTERIA	F	44
BACTERIA	F	43
BACTERIAL INFECTIONS	A	120
BACTERIAL INFECTIONS	A	91
BEHCET'S SYNDROME	A	96
BEHCET'S SYNDROME	A	93
BEHCET'S SYNDROME	A	26
BEHCET'S SYNDROME	A	27
BIOCHEMISTRY	B	71
BIOCHEMISTRY	C	2
BIOCHEMISTRY	C	1
BIOCHEMISTRY	C	10
BIOLOGICAL TRANSPORT	B	57
BLOOD PLATELETS	E	89
BLOOD VESSELS	E	9
BLOOD	E	8
BLOOD	E	1
BLOOD	E	6
BLOOD	E	34
BLOOD	E	51
BLOOD	E	89
BLOOD	E	91
BLOOD	A	120

SUBJECT AREA		PAGE
BONE AND BONES	E	75
BONE AND BONES	E	47
BONE AND BONES	E	12
CALCIUM PHOSPHATES	D	70
CALCIUM PHOSPHATES	D	90
CALCIUM RADIOSOTOPES	D	119
CARBOHYDRATES	D	7
CATS	F	20
CELL DIVISION	B	54
CELLS	E	109
CEPHALOMETRY	C	5
CHEMISTRY, PHYSICAL	B	76
CHEMORECEPTORS	E	3
CHEMOTAXIS	B	6
CHEMOTAXIS	B	60
CHEMOTAXIS	B	48
CHEMOTAXIS	B	42
CHICKENS	F	35
CHILDREN	F	29
CHILDREN	F	32
CHILDREN	F	73
CHILDREN	F	72
CHILDREN	F	50
CHILDREN	F	37
CHILDREN	F	65
CHILDREN	F	19
CHILDREN	F	16
CHILDREN	F	15
CHILDREN	F	13
CHILDREN	F	81
CHILDREN	F	126
CHILDREN	F	127
CHILDREN	F	102
CHILDREN	F	101
CHROMATOGRAPHY	C	108
CHROMATOGRAPHY	C	53
CLASSIFICATION	B	23
CLEFTS	A	59
CLEFTS	A	5
CLEFTS	A	16
CLEFTS	A	101

SUBJECT AREA		PAGE
CLINICAL TRIALS	C	72
CLINICAL TRIALS	C	32
CLINICAL TRIALS	C	29
CLINICAL TRIALS	C	27
CLINICAL TRIALS	C	37
CLINICAL TRIALS	C	73
CLINICAL TRIALS	C	99
CLINICAL TRIALS	C	111
CLINICAL TRIALS	C	114
CLINICAL TRIALS	C	104
CLINICAL TRIALS	C	88
CLINICAL TRIALS	C	115
CLINICAL TRIALS	C	93
CLINICAL TRIALS	C	129
COLLAGEN	D	25
COLLAGEN	D	10
COLLAGEN	D	2
COLLAGEN	D	9
COMPLEMENT	D	63
COMPUTERS	C	58
COMPUTERS	C	18
COMPUTERS	C	30
COMPUTERS	C	31
COMPUTERS	C	41
COMPUTERS	C	45
CONCANAVALIN A	D	69
CONCANAVALIN A	D	97
CONNECTIVE TISSUE DISEASES	A	26
CONNECTIVE TISSUE DISEASES	A	9
CONNECTIVE TISSUE	E	9
CONNECTIVE TISSUE	E	59
CONNECTIVE TISSUE	E	10
CORN	D	60
CRYOGLOBULINS	D	26
CYANCOBALAMIN	D	118
CYCLOPHOSPHAMIDE	D	127
CYSTIC FIBROSIS	A	78
CYTOCHEMISTRY	C	28
CYTOTOXICITY	B	61
DEATH	A	109
DEATH, SUDDEN	A	81
DENTAL CARIES	A	83
DENTAL CARIES	A	72
DENTAL CARIES	A	29
DENTAL CARIES	A	32

SUBJECT AREA		PAGE
DENTAL CARIES	A	84
DENTAL CARIES	A	52
DENTAL CARIES	A	73
DENTAL CARIES	A	40
DENTAL CARIES	A	37
DENTAL CARIES	A	105
DENTAL CARIES	A	117
DENTAL CARIES	A	118
DENTAL CARIES	A	106
DENTAL ENAMEL HYPOPLASIA	A	15
DENTAL ENAMEL	E	15
DENTAL PALQUE	A	98
DENTAL PLAQUE	A	124
DENTAL PLAQUE	A	33
DENTAL PLAQUE	A	66
DENTITION	E	19
DEVELOPMENT	B	13
DEVELOPMENT	B	74
DEVELOPMENT	B	24
DIABETES MELLITUS	A	113
DIAGNOSIS	C	68
DICTYOSTELIUM DISCOIDEUM	F	56
DIET	C	79
DISCRIMINATION	B	49
DMF	C	100
DNA	D	54
ELASTIN	D	2
ELASTIN	D	9
ELECTROLYTES	D	36
ELECTROPHORESIS	C	108
EMBRYO	E	102
EMBRYO	E	109
EMBRYOLOGY	B	38
ENDOCRINE DISEASES	A	82
ENDOCRINE GLANDS	E	82
ENDOTOXINS	D	62
ENDOTOXINS	D	128
ENZYMES	E	56
ENZYMES	D	7
ENZYMES	E	1
ENZYMES	E	51
ENZYMES	D	17
EPIDEMIOLOGY	B	84
EPITHELIAL CELLS	E	95
EPITHELIAL CELLS	E	110

SUBJECT AREA		PAGE
EVOLUTION	B	22
EXOCRINE GLANDS	E	28
EXOCRINE GLANDS	E	82
EXPLANTATION	C	110
FACE	E	13
FACE	E	38
FAMILY	F	5
FECES	E	65
FETUS	E	50
FETUS	E	13
FETUS	E	81
FIBROUS DYSPLASIA OF BONE	A	21
FISHES	F	10
FIXATION	C	71
FLUORESCENT ANTIBODY TECHNIC	C	94
FLUORESCENT ANTIBODY TECHNIC	C	33
FLUORESCENT ANTIBODY TECHNIC	C	129
FLUORIDATION	C	29
FLUORIDES	D	32
FLUORIDES	D	73
FLUORIDES	D	72
FLUORIDES	D	15
FLUORIDES	D	40
FLUORIDES	D	117
FLUORIDES	D	119
FLUOROSIS	A	29
FOLIC ACID	D	17
GANGLIA	E	125
GENETICS	B	14
GENETICS	B	24
GENETICS	B	5
GENETICS	B	4
GENETICS	B	3
GERM-FREE LIFE	B	103
GESTATION	B	74
GINGIVA	E	60
GLUCOSYLTRANSFERASES	D	52
GLYCOPROTEINS	D	108
GNOTOBIOTICS	B	103
GRAFTS	C	123
GROWTH	B	38
GROWTH	B	55
GROWTH	B	54
GROWTH	B	8
GROWTH	B	74

SUBJECT AREA		PAGE
GUINEA PIGS	F	61
HAWAIIANS	F	14
HEAD	E	50
HERPES SIMPLEX	A	85
HERPES SIMPLEX	A	92
HERPES SIMPLEX	A	94
HERPES SIMPLEX	A	112
HERPES SIMPLEX	A	125
HISTAMINE LIBERATION	C	34
HISTOCHEMISTRY	B	17
HODGKIN'S DISEASE	A	42
HUMAN	F	42
HUMAN	F	73
HUMAN	F	37
HUMAN	F	50
HUMAN	F	17
HUMAN	F	19
HUMAN	F	111
HUMAN	F	91
HUMAN	F	14
HUMAN	F	11
HUMAN	F	78
HUMAN	F	34
HUMAN	F	84
HUMAN	F	29
HUMAN	F	89
HUMAN	F	32
HUMAN	F	27
HUMAN	F	21
HUMAN	F	114
HUMAN	F	3
HUMAN	F	88
HUMAN	F	115
HUMAN	F	65
HUMAN	F	93
HUMAN	F	4
HUMAN	F	72
HUMAN	F	122
HUMAN	F	120
HUMAN	F	129
HUMAN	F	123
HUMAN	F	121
HUMAN	F	126
HUMAN, POPULATION RESEARCH	F	5
HUMANS	F	26
HUMANS	F	49

SUBJECT AREA		PAGE
HYDROXYAPATITE	D	105
HYPERLASIA	A	11
HYPOPHOSPHATEMIA	A	19
IGE	D	116
IMMUNOCHEMISTRY	B	53
IMMUNOGENETICS	B	110
IMMUNOLOGY	B	87
IMMUNOLOGY	B	92
IMMUNOLOGY	B	116
IMMUNOLOGY	B	61
IMMUNOLOGY	B	89
IMMUNOLOGY	B	97
IMMUNOLOGY	B	52
IMMUNOLOGY	B	86
IMMUNOLOGY	B	27
IMMUNOLOGY	B	85
IMMUNOLOGY	B	110
IMMUNOLOGY	B	34
IMMUNOLOGY	B	129
IMPLANTATION	C	130
INDIANS, NORTH AMERICAN	F	4
INDIANS, NORTH AMERICAN	F	14
INDICATORS & REAGENTS	D	71
INFECTION	A	125
INFLAMMATION	A	60
INFLAMMATION	A	63
INFLAMMATION	A	9
INFLAMMATION	A	34
INFLAMMATION	A	89
INFLAMMATION	A	48
INFORMATION RETRIEVAL	C	45
ISOENZYMES	D	78
ISOENZYMES	D	113
K-CELLS	E	61
KERATIN	D	95
KERATOSIS	A	11
LACTIC ACID	D	7
LAVAGE	C	121
LECITHINS	D	36
LECTINS	D	69
LEUCOCYTES	E	6
LUNG	E	9
LUNG	A	81
LYMPHOCYTES	E	97
LYMPHOCYTE TRANSFORMATION	B	129

SUBJECT AREA		PAGE
LYMPHOCYTES	E	8
LYMPHOCYTES	E	86
LYMPHOCYTES	E	62
LYMPHOCYTES	E	61
LYMPHOCYTES	E	53
LYMPHOCYTES	E	55
LYMPHOCYTES	E	35
LYMPHOCYTES	E	42
LYMPHOCYTES	E	85
LYMPHOCYTES	E	48
LYMPHOCYTES	E	47
LYMPHOKINES	D	42
LYMPHOKINES	D	35
LYMPHOMA	A	42
MACROMOLECULAR SYSTEMS	D	59
MACROPHAGES	E	61
MACROPHAGES	E	128
MACROPHAGES	E	47
MALFORMATIONS	A	4
MALFORMATIONS	A	127
MALFORMATIONS	A	38
MALFORMATIONS	A	24
MALOCCLUSION	A	14
MANNITOL	D	57
MEDICAL ILLUSTRATION	C	50
METABOLIC DISEASES	A	19
METABOLISM	B	43
METABOLISM	B	7
MICE	F	116
MICE	F	62
MICE	F	122
MICE	F	86
MICE	F	82
MICE	F	110
MICE	F	38
MICE	F	85
MICE	F	17
MICE	F	24
MICE	F	113
MICROMANIPULATION	C	102
MICROORGANISMS	F	33
MICROORGANISMS	F	45
MICROSCOPY	C	94
MICROSCOPY	C	20
MICROSCOPY	C	71

SUBJECT AREA		PAGE
MICROSCOPY	C	108
MICROSCOPY	C	80
MICROSCOPY, ELECTRON	C	64
MICROSCOPY, ELECTRON	C	80
MICROSCOPY, ELECTRON	C	20
MICROSCOPY, ELECTRON	C	76
MINERALS	D	76
MINERALS	D	75
MINORITY GROUPS	F	4
MITOGENS	D	128
MONKEYS	F	83
MONKEYS	F	64
MONKEYS	F	20
MONKEYS	F	18
MONKEYS	F	80
MONKEYS	F	130
MONKEYS	F	49
MONKEYS	F	41
MOTTLED ENAMEL	A	29
MOUTH MUCOSA	E	11
MOUTHWASHES	D	73
NBT TEST	C	91
NEOPLASMS	A	21
NEUROLOGY	B	27
NEUROPHYSIOLOGY	B	31
NEWBORN	E	126
NIDATION	B	102
NUCLEAR MAGNETIC RESONANCE	B	2
NUTS	D	60
ODORS	B	3
OSTEITIS	A	121
PAIN	A	20
PAIN	A	41
PAIN	A	49
PALATE	E	95
PALATE	E	109
PALATE	F	74
PALATE	E	16
PALATE	E	108
PALATE	E	101
PALATE	E	59
PANCREAS	E	113
PAROTID GLAND	E	28
PAROTID GLAND	E	77
PERCEPTION	B	81

SUBJECT AREA		PAGE
PERIODONTAL DISEASE	A	33
PERIODONTAL DISEASE	A	35
PERIODONTIUM	E	17
PHOSPHOROFLUORIDATE	D	70
PHOSPHOTRANSFERASES	D	57
PHOTOGRAPHY	C	56
PHYOLGENY	B	22
PILOCARPINE	D	77
PLANT AGGLUTININS	D	97
POLYSACCHARIDES	D	69
POLYSACCHARIDES	D	44
POLYSACCHARIDES	D	52
POPULATION RESEARCH	C	14
POPULATION RESEARCH	C	4
POPULATION RESEARCH	C	5
PRECANCEROUS CONDITIONS	A	11
PRECANCEROUS CONDITIONS	A	21
PROTEINS	D	71
PROTEINS	D	55
PROTEINS	D	76
PROTOZOA	F	56
PROTOZOA	F	6
PSEUDOHYPOPARATHYROIDISM	A	19
RABBITS	F	89
RABBITS	F	127
RADIOGRAPHY	C	5
RADIOGRAPHY, DENTAL	C	68
RADIOGRAPHY, DENTAL	C	67
RATS	F	59
RATS	F	106
RATS	F	119
RATS	F	117
RATS	F	79
RATS	F	40
RATS	F	20
RATS	F	15
RATS	F	103
RATS	F	118
RATS	F	16
RATS	F	28
RATS	F	127
RESPIRATORY TRACT DISEASES	A	81
RIBOSOMES	E	55
RNA	D	8
RNA	D	25
SALIVA	E	77

SUBJECT AREA		PAGE
SALIVARY GLAND NEOPLASMS	A	17
SALIVARY GLANDS	E	28
SALIVARY GLANDS	E	113
SALIVARY GLANDS	E	53
SALIVARY GLANDS	E	77
SEMEN	E	51
SENSATION	B	80
SENSATION	B	64
SENSATION	B	126
SENSATION	B	81
SENSATION	B	20
SIALOGRAPHY	C	77
SJOGREN'S SYNDROME	A	96
SJOGREN'S SYNDROME	A	53
SJOGREN'S SYNDROME	A	122
SJOGREN'S SYNDROME	A	87
SJOGREN'S SYNDROME	A	77
SKIN	E	123
SKIN	E	80
SLIME MOLD	F	6
SPECTROPHOTOMETRY	C	76
SPECTROPHOTOMETRY, INFRARED	C	76
SPECTRUM ANALYSIS	C	12
STATISTICS	C	104
STATISTICS	C	100
STATISTICS	C	99
STEEPTOCOCCUS	F	118
STERIODS	D	88
STOMATITIS, APHTHOUS	A	88
STOMATITIS, APHTHOUS	A	96
STOMATITIS, APHTHOUS	A	93
STREPTOCOCCUS	F	65
STREPTOCOCCUS	F	66
STREPTOCOCCUS	F	124
STREPTOCOCCUS	F	119
STREPTOCOCCUS	F	57
STREPTOCOCCUS	F	7
STREPTOCOCCUS	F	117
STREPTOCOCCUS	F	69
STREPTOCOCCUS	F	79
STREPTOCOCCUS	F	98
STREPTOCOCCUS	F	103
STREPTOCOCCUS	F	111
STREPTOCOCCUS	F	52
STREPTOCOCCUS	F	44
STREPTOCOCCUS	F	43
STREPTOCOCCUS	F	83

SUBJECT AREA		PAGE
SUCRASE	D	43
SUCROSE	D	43
SUCROSE	D	44
SURGERY	C	120
SURGERY	C	121
TASTE	B	3
TASTE	B	126
TAXONOMY	B	23
TELECOMMUNICATION	C	30
TELEVISION	C	126
TERATOGENESIS	B	102
TERATOGENS	D	13
TERATOGENS	D	16
TERATOGENS	D	74
TERATOID TUMOR	A	102
TETRACYCLINE	D	15
TETRACYCLINE	D	75
TETRACYCLINE	D	88
THERAPEUTICS	C	27
TONGUE	E	126
TOOTH	E	12
TRACE ELEMENTS	D	101
TRANSGLUTAMINASES	E	51
TRANSGLUTAMINASES	E	1
TRANSMISSION	B	79
TRANSPLANTATION	C	102
TRANSPLANTATION	C	123
TRANSPORT	B	57
TRIGEMINAL NERVE	E	64
TRIGEMINAL NERVE	E	41
TRIGEMINAL NERVE	E	18
UREMIA	A	75
UTRASONICS	C	124
VACCINES	D	83
VAGINAL DISEASES	A	125
VIRUS DISEASES	A	125
VIRUS DISEASES	A	93
VIRUS DISEASES	A	112
VIRUS DISEASES	A	94
VIRUSES	F	125
VIRUSES	F	112
VIRUSES	F	96
VIRUSES	F	82
VITAMIN B 12	D	118
WOUND HEALING	B	51
X-RAY DIFFRACTION	C	36
X-RAY DIFFRACTION	C	75
XEROSTOMIA	A	77

NIDR ANNUAL REPORT - FY 74

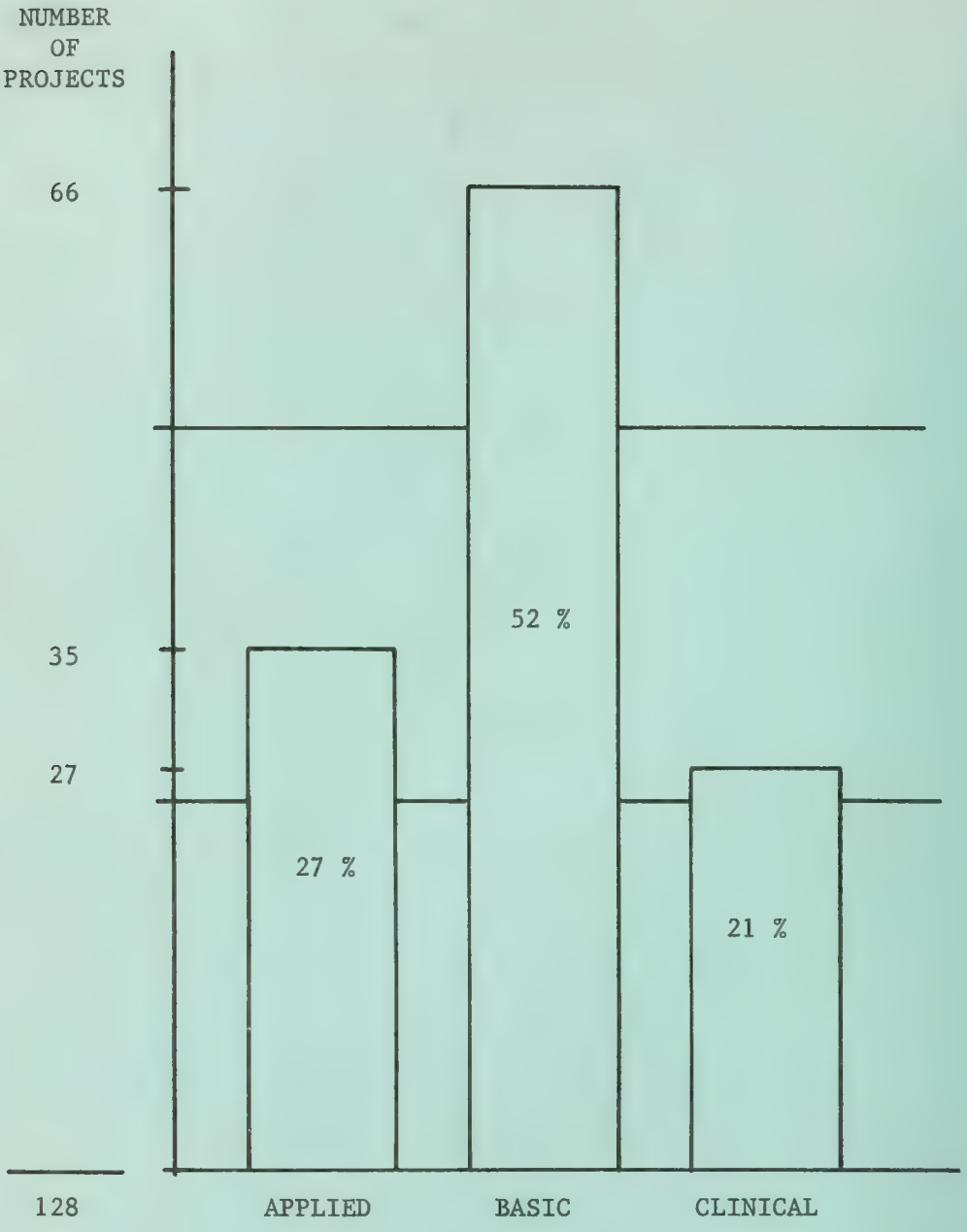
INDEX

RESEARCH PROJECTS BY TYPE OF RESEARCH

Type of Research	Page Numbers
APPLIED	3-4-5-11-13-14-16-19-30-31-32-40-45-49-58-66-74-79-81-83-84-95-99-100-101-102-103-104-105-106-117-118-119-124-127
	Total 35 Projects (27%)
BASIC	1-2-6-7-8-9-10-12-15-17-18-20-22-23-24-25-28-33-34-35-36-38-41-42-43-44-48-50-51-52-54-55-56-57-59-60-61-62-63-64-65-69-70-71-75-76-80-82-85-86-89-90-92-94-96-97-107-108-109-110-112-113-116-125-126-128
	Total 66 Projects (52%)
CLINICAL	21-26-27-29-37-47-53-67-68-72-73-77-78-87-88-91-93-98-111-114-115-120-121-122-123-129-130
	Total 27 Projects (21%)

By type of research as designated by the principal investigator.

RESEARCH PROJECTS BY TYPE OF RESEARCH



By type of research as designated by the principal investigator.

NATIONAL INSTITUTE OF DENTAL RESEARCH

Classification Guide

CATEGORIES and SUBJECTS

CATEGORY A

DISEASES AND DISORDERS

AMLOIDOSIS
AUTOIMMUNE DISEASES
BACTEREMIA
BACTERIAL INFECTIONS
BEHCET'S SYNDROME
BLOOD
CARCINOMA
CARIES, DENTAL
CARIES, ROOT
CLEFTS
CONNECTIVE TISSUE DISEASES
CYSTIC FIBROSIS
DEAFNESS
DEATH
DENTAL CALCULUS
DENTAL CARIES
DENTAL ENAMEL HYPOPLASIA
DENTAL PLAQUE
DIABETES
DIABETES MELLITUS
ENDOCRINE DISEASES
ETIOLOGY
FLUOROSIS
FIBROUS DYSPLASIA OF BONE
GENETIC DISORDERS
GINGIVAL HYPERPLASIA
GINGIVITIS
HEREDITARY DISEASES
HERPES SIMPLEX
HODGKIN'S DISEASE
HYPERPLASIA
HYPERSENSITIVITY, DELAYED
HYPOPHASPHATEMIA
INFECTION
INFLAMMATION
KERATOSIS
LEUKEMIA
LEUKODEMA
LUNG
LYMPHOMA
MALFORMATIONS
MALOCCLUSION
METABOLIC DISEASES
MONOCYTES
MOTTLED ENAMEL
NEOPLASMS
NUTRITION DISORDERS
ODONTOGENIC TUMOR
OSTEITIS
PAIN
PERIODONTAL DISEASES
PRECANCEROUS CONDITIONS
PSEUDOHYPOPARATHYROIDISM
RESPIRATORY TRACT DISEASES
ROOT CARIES
SALIVARY GLAND NEOPLASMS
SARCOIDOSIS
SJOGREN'S SYNDROME
SKULL FRACTURES
STOMATITIS, APHTHOUS
SUBMUCOUS FIBROSIS
TERATOID TUMOR
TRIGEMINAL NEURALGIA
UREMIA
VAGINAL DISEASES
VIRUS DISEASES
XEROSTOMIA

CATEGORY B

FIELDS OF SCIENCE AND RELATED SUBJECTS

AGING
AMINO ACID SEQUENCE
ANATOMY
ANESTHESIOLOGY
ANTHROPOLOGY
ANTIBODY FORMATION
BIOCHEMISTRY
BIOLOGICAL TRANSPORT
BIOLOGY
BIOMEDICAL ENGINEERING
BIOPHYSICS
BIOSYNTHESIS
BLOOD COAGULATION
CELL DIVISION
CHEMISTRY
CHEMISTRY, PHYSICAL
CHEMISTRY, PROTEIN
CHEMOTAXIS
CLASSIFICATION
COAGULATION
COMPUTER SCIENCE
CRYSTALLIZATION
CYTOLOGY
CYTOTOXICITY
DELIVERY OF HEALTH CARE
DENTAL OCCLUSION
DENTISTRY, PREVENTIVE
DEVELOPMENT
DISCRIMINATION
ELECTROPHORESIS, DISK
ELECTRON SPIN RESONANCE
EMBRYOLOGY
ENZYMOLOGY
EPIDEMIOLOGY
EVOLUTION
FERMENTATION
FLOW RATES
GESTATION
GENETICS
GERM-FREE LIFE
GNOTOBIOTICS
GRAFT VS HOST REACTION
GROWTH
HEMODYNAMICS
HEURISTICS
HISTAMINE LIBERATION
HISTOCHEMISTRY
HISTOCOMPATIBILITY
HISTOLOGY
HISTOLOGY, COMPARATIVE
HISTOPATHOLOGY
IMMUNE TOLERANCE
IMMUNITY
IMMUNOCHEMISTRY
IMMUNOGENETICS
IMMUNOLOGY
INHIBITION
LIPOLYSIS
LYMPHOCYTE TRANSFORMATION
KINETICS
MATERNAL-FETAL EXCHANGE
MEDICINE
METABOLISM
MICROBIOLOGY
MOTOR ACTIVITY
NEUROLOGY
NEUROPHYSIOLOGY
NIDATION
NUCLEAR MAGNETIC RESONANCE
NUTRITION
ODORS
ORTHODONTICS
PATHOLOGY
PERCEPTION
PERIODONTICS
PHARMACOLOGY
PHYLOGENY
PHYSIOLOGY
RHEUMATOLOGY
SEGREGATION
SENSATION
SPEECH
STOMATOLOGY
SURGERY, ORAL
TASTE
TAXONOMY
TERATOGENESIS
TERATOLOGY
TRANSPORT
VIROLOGY
WOUND HEALING
ZOOLOGY

CATEGORY C

TECHNICS AND EQUIPMENT

ANALYSIS
ANESTHESIA
ANTIGEN-ANTIBODY REACTIONS
ATLASES
AUTOANALYSIS
AUTOMATION
AUTORADIOGRAPHY
BACTERIOLOGY
BIOCHEMISTRY
BIOMETRY
BIOPSY
BIOSYNTHESIS
CANNULATION
CEPHALOMETRY
CHARACTERIZATION
CHEMISTRY
CHEMISTRY, PHYSICAL
CHEMOTOGRAPHY
CHROMATOGRAPHY
CHROMATOGRAPHY, GAS
CLASSIFICATION
CLINICAL TRIALS
COMPLEMENT FIXATION TESTS
COMPUTERS
CYTOCHEMISTRY
CYTODIAGNOSIS
DEMOGRAPHY
DENSITOMETRY
DENTAL IMPLANTATION
DENTAL PROPHYLAXIS
DIAGNOSIS
DIET
DISSECTION
DMF INDEX
DRUG THERAPY
ELECTROCARDIOGRAPHY
ELECTROENCEPHALOGRAPHY
ELECTRON PROBE MICROANALYSIS
ELECTROPHORESIS
EXAMINATION
EXODONTIA
EXPLANTATION
FLOW RATES
FIXATION
FLUORESCENT ANTIBODY TECHNIC
FLUORIDATION
FLUOROMETRY
FREEZE-ETCHING
GRAFTS
HEMODYNAMICS
HISTAMINE LIBERATION
HISTOCOMPATIBILITY TESTING
HISTOCYTOCHEMISTRY
HISTOLOGICAL TECHNICS
HYPERSENSITIVITY
IMMUNOASSAY
IMPLANTATION
INFORMATION RETRIEVAL
LAVAGE
LYMPHOCYTE TRANSFORMATION
MEDICAL ILLUSTRATION
MICROINCINERATION
MICROMANIPULATION
MICRORADIOGRAPHY
MICROSCOPY
MICROSCOPY, ELECTRON
MICROSCOPY, FLUORESCENCE
MODELS, THEORETICAL
MOTION PICTURES
NBT TEST
OSTEOTOMY
PERFUSION
PHOTOGRAPHY
PHYSICS
POLYGRAPH
PRECIPITATION
PSYCHIATRIC CONSULTATION
PURIFICATION
RADIOAUTOGRAPHY
RADIOGRAPHY
RADIOGRAPHY, DENTAL
RADIOIMMUNOASSAY
SCINTILLATION
SIALOGRAPHY
SPECTROPHOTOMETRY
SPECTRUM ANALYSIS
STATISTICS
STEREOGNOSIS
SURGERY
TACTILE STIMULATION
TELECOMMUNICATION
TELEVISION
THERAPEUTICS
TOMOGRAPHY
TONGUE TRACKING
TRANSDUCER
TRANSPLANTATION
ULTRASONICS
VACCINATION
X-RAY DIFFRACTION

CATEGORY D

BIOMATERIALS, CHEMICALS, AND DRUGS

ACTINOBOLIN
ADENOSINE MONOPHOSPHATE
ADHESIVE SEALANTS
AGAR
AMINO ACIDS
AMYLASE
AMYLOID
ANTIBODIES
ANTICARIES AGENTS
ANTIGENS
ANTIHISTAMINICS
ANTI-INFECTIVE AGENTS
ANTIMICROBIAL
ANTIPLAQUE AGENTS
ANTISEROTONIN
ANTITHYMOCYTE SERUM
APATITES
CALCIUM PHOSPHATES
CALCIUM RADIOISOTOPES
CARBOHYDRATES
CARCINOGENS
CERAMICS
COMPLEMENT
COLLAGEN
CONCONAVALIN A
CORN
CORTICOSTERONE
CRYOGLOBULINS
DENTAL AMALGAM
DEXTRAN
DNA
ELASTIN
ELECTROLYTES
ENDOTOXINS
ENZYMES
FLUORIDES
FOLIC ACID
GAMMA GLOBULIN
GLUCOSYLTRANSFERASES
GLYCOPROTEINS
HEMOGLOBIN
HEXITOLS
HORMONES
HYDROXYAPATITE
IGE
IMMUNE SERUMS
INDICATORS AND REAGENTS
INHIBITORS
IONS
ISOENZYMES
KERATIN
LACTIC ACID
LECITHINS
LECTINS
LYMPHOKINES
MACROMOLECULAR SYSTEMS
MANNITOL
METALS
MINERALS
MITOGENS
MOUTHWASHES
MUCOPOLYSACCHARIDSS
NUTS
PEPTIDES
PHOSPHATES
PHOSPHOFLUORIDATE
PHOSPHOLIPIDS
PHOSPHOTRANSFERASES
PILOCARPINE
PLANT AGGLUTININS
POLYMYXIN
POLYSACCHARIDES
POLYSACCHARIDES, BACTERIAL
PROTEINS
RNA
STEROIDS
SUCROSE
TABLETS
TERATOGENS
TETRACYCLINE
TISSUE FACTOR
TOOTH, ARTIFICIAL
TRACE ELEMENTS
TRANSGLUTAMINASES
VACCINES
VITAMIN B 12
WALNUTS
ZIRCONIUM

CATEGORY E

ANATOMICAL TERMS

AMELOBLASTS
AMNIOTIC FLUID
BASOPHILES
BLOOD
BLOOD PLATELETS
BLOOD VESSELS
BONE AND BONES
CARTILAGE
CELLS
CELLS, CULTURES
CENTRAL NERVOUS SYSTEM
CHEMORECEPTORS
CHICK EMBRYO
CONNECTIVE TISSUE
DENTAL ENAMEL
DENTAL PULP
DENTIN
DENTITION
EMBRYO
ENDOCRINE GLANDS
ENZYMES
EPITHELIAL CELLS
EXOCRINE GLANDS
FACE
FACE, EMBRYONIC
FECES
FETUS
GANGLIA
GENITALIA
GINGIVA
HAIR
HEAD
INTERCELLULAR JUNCTIONS
JAW
K-CELLS
LEUKOCYTES
LIP
LUNG
LYMPHOCYTES
LYSOSOMES
MACROPHAGES
MANDIBLE
MAST CELLS
MONOCYTES
MOUTH
MOUTH MUCOSA
MUSCLE
NEWBORN
PALATE
PANCREAS
PAROTID GLAND
PERIODONTIUM
PERIPHERAL NERVOUS SYSTEM
PHARYNX
PLEURAL FLUID
RIBOSOMES
SALIVA
SALIVARY GLANDS
SEMEN
SKIN
SKULL
SPLEEN
SYNAPSES
TEMPORAMANDIBULAR JOINT
TENDONS
THYMUS GLAND
TISSUE, CONNECTIVE
TISSUE, DIFFERENTIATING
TISSUE, MINERALIZED
TONGUE
TOOTH
TRIGEMINAL NERVE
VELUM

CATEGORY F

ORGANISMS AND NAMED GROUPS OF PEOPLE

ACTINOMYCES
ADULT
ASCARIS
BACTERIA
CHICKENS
CATS
CHILD
CLINICAL CENTER PATIENTS
DICTYOSTELIUM DISCOIDEUM
DOGS
FAMILY
FISHES
GUINEA PIGS
HAMSTERS
HAWAIIANS
HUMAN
HUMAN, FEMALES
HUMAN, INFANTS
HUMAN, INFANTS, NEWBORN
HUMAN, MALES
HYDRA
INDIANS, NORTH AMERICAN
INDIANS, SOUTH AMERICAN
INFANT
MAMMALS
MICE
MICROORGANISMS
TRANSGLUTAMINASES
MOLLUSCA
MONKEYS
NEGROES
PROTOZOA
RABBITS
RATS
RODENTS
TAENIA
VIRUSES

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBC302b52

NIDR-52B- 001

TITLE OF PROJECT

Chemical, Stereochemical and Conformational Aspects of Transglutaminases

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: J. E. Folk Chief, Enzyme Chem. S. LB NIDR
OTHER: M. A. Gross Staff Fellow LB NIDR

COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biochemistry
Section: Enzyme Chemistry
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Active site mapping studies on transglutaminases using model substrates will continue with special emphasis on the blood coagulation transglutaminases (plasma and platelet factor XIII). Active site mapping of transglutaminases using alkyl isocyanates which irreversibly inhibit the enzymes is in progress. Studies are also in progress on the amine specificity of the enzymes using straight- and branched-chain aliphatic amines and peptide derivatives of lysine and its analogs. Investigations of the γ-glutamyl esterase and ester synthetase activities of guinea pig liver transglutaminase are also currently in progress. It is the purpose of these studies to relate the structures and mechanisms of these enzymes to their catalytic function.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 20325
TOTAL MAN YEARS: 2.25
PROFESSIONAL: 1.25
OTHER: 1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	J. E. Folk	5/8/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBC101b52

NIDR-52B -002

TITLE OF PROJECT

Structural Studies on Collagen

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	K. A. Piez	Chief	LB NIDR
OTHER:	D. A. Torchia	Guest Worker	LB NIDR

COOP: National Bureau of Standards
Laboratory of Molecular Biophysics, Oxford University

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biochemistry
Section: Protein Chemistry
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

It is the long range purpose of this project to study the structure of collagen at various levels and correlate with function. The topics of present interest are:

1. Electron optical studies of native collagen aggregates. Electron microscopy with the aid of optical diffraction analysis of the plates is being used to study fibril structure and fibrillogenesis.

2. The conformation of collagen. Nuclear magnetic resonance studies on well characterized peptides from collagen should contribute to an understanding of several structural features such as side chain interactions and hydrogen bonding.

3. The three-dimensional structure of collagen. Computer analysis of the primary structure of the polypeptide chains in collagen is being done to understand the origins of molecular packing.

4. The structure of elastin. Nuclear magnetic resonance is being used to measure the mobility of the polypeptide chains in elastin and elucidate the mechanism of elasticity of elastin fibers.

SPECIAL DESCRIPTORS:	Tooth Structure and Composition
NIDR CLASSIFICATION:	10300
TOTAL MAN YEARS:	1.00
PROFESSIONAL:	1.00
OTHER:	0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Karl A. Piez	5/10/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-HGB001a54

NIDR-54A- 003

TITLE OF PROJECT

Genetics of Chemoreception Thresholds

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Brown, Kenneth S.	Medical Director	HGB	NIDR
OTHER:	Leyshon, Webster C.	Biologist	HGB	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Human Genetics Branch
Section: Developmental Genetics
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this study are to describe experimentally the variation between individuals in their detection thresholds for odors and tastes and to analyze the variation genetically and statistically to determine the nature of the components that contribute to this variation.

Several methods are being utilized. A statistical study of the components of variation in the detection thresholds of a variety of odors in a group of normal individuals is directed to identifying chemical groups that show common patterns of odor threshold. Family and twin studies are directed at detecting the contribution of genetic components of variability and at the study of any specific segregating traits.

Preliminary studies of school age children have been directed at detecting pure chemicals which have odors that are certainly detected by some children at a standard concentration but not by others. Efforts have been directed at a reproducable but rapid screening method by which to identify compounds with significant bimodality of threshold. When such methodology and compounds are identified family studies will be carried out.

SPECIAL DESCRIPTORS:	Human
NIDR CLASSIFICATION:	41323
TOTAL MAN YEARS:	.50
PROFESSIONAL:	.50
OTHER:	.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Kenneth S. Brown	3/25/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-HGB007a58

NIDR-58A- 004

TITLE OF PROJECT

Congenital Malformation and Birth Characteristics of American Indians

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Niswander, Jerry D.	Dental Director Chief of HGB	HGB	NIDR
OTHER:	Iba, Barbara Y.	Geneticist-Human Medical	HGB	NIDR
	Bingle, Glenn J.	Surgeon	HGB	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Human Genetics Branch
Section: Population Genetics
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This study is based on approximately 45,000 clinical newborn records from forty-six Public Health Service Hospitals to ascertain the total (at birth) frequency of congenital malformation among American Indians as well as frequencies of specific major defects. These data are compared to those obtained from other Mongoloid and Caucasoid populations. A major objective of this study is to examine the effect of tribal background and Caucasion admixture on variation in malformation rates. Several medical, culture and socio-economic variables are included as indicators of environmental effects. Birth weight and twinning rates are examples of other birth characteristics being analyzed.

SPECIAL DESCRIPTORS: Human, Population Research
NIDR CALSSIFICATION: 41100
TOTAL MAN YEARS: 1.50
PROFESSIONAL: .75
OTHER: .75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Jerry D. Niswander

DATE: 3/25/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DAT

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-HGB009a58

NIDR-58A- 005

TITLE OF PROJECT

Characteristics of Families with Oral Clefts

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Niswander, Jerry D.	Dental Director Chief of HGB	HGB	NIDR
COPI:	Johnston, Malcolm C.	Visiting Scientist	HGB	NIDR
OTHER:	Iba, Barbara Y.	Geneticist-Human Medical	HGB	NIDR
	Kurisu, Kojiro	Visiting Scientist	HGB	NIDR
	Bingle, Glenn J.	Surgeon	HGB	NIDR
COOP:	Lancaster Cleft Palate Clinic, Lancaster, PA			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Human Genetics Branch
Section: Population Genetics
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This project is designed to determine 1) if there are physical stigmata particularly changes in facial morphology associated with oral clefts, which are familial in nature and may be useful in clarifying the role of genetic (and environmental) factors in the etiology and pathogenesis in these anomalies. Of particular interest is the study of various characteristics obtained from cephalometric radiographs of affected individuals as well as their "normal" relatives including twins. Other objectives are 2) to develop methods to identify and classify heterogeneous subtypes of oral clefts and to identify individuals who are genetically at high risk, 3) to determine if maternal factors play a significant role in the etiology of oral clefts and 4) to study the incidence, type and significance of cardiovascular anomalies in patients with clefts.

SPECIAL DESCRIPTORS: Human, Population Research
NIDR CLASSIFICATION: 42240
TOTAL MAN YEARS: 3.00
PROFESSIONAL: 1.75
OTHER: 1.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Jerry D. Niswander	3/25/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBC202b61

NIDR-61B- 006

TITLE OF PROJECT

Studies on Chemotaxis

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Elliott Schiffmann Chemist, Conn. Tissue S. LB NIDR

OTHER: None

COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biochemistry
Section: Connective Tissue
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

It is proposed to gain insight into the biochemical processes of cell migration along a chemical gradient. Cells such as leucocytes, bacteria, and the slime mold have the property of responding to their environment in this manner. Some progress has been achieved in the isolation and characterization of compounds exuded from an E. coli strain which are chemotactic for leucocytes. Evidence has been obtained on the composition of these compounds which are peptides of small molecular weight. The material from E. coli appears to compete for the cell with a chemotactic substance derived from complement. With the aid of various inhibitors some information has been obtained on the requirements of the leucocyte for chemotaxis. It is hoped that by a study of the direct interaction of chemotactic factors with white cells some understanding of the directed movement of cells would be gained.

SPECIAL DESCRIPTORS: Blood
NIDR CLASSIFICATION: 20312
TOTAL MAN YEARS: 2.00
PROFESSIONAL: 1.00
OTHER: 1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	E Schiffmann	5/8/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LMI013b61

NIDR-61B-007

TITLE OF PROJECT

Studies on the Regulation of Carbohydrate Metabolism and Lactic Acid Production in Oral Microorganisms

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Dr. Charles L. Wittenberger	Research Microbiologist	LMI	NIDR
OTHER:	Mrs. M. P. Palumbo	Chemist	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section : Microbial Physiology
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The mechanisms by which cariogenic and noncariogenic Streptococci and certain members of the genus Actinomyces regulate the distribution of substrate carbon among multiple catabolic pathways is under investigation. Several enzymes, which function in the constitutive pathways that lead to lactic acid, have been identified as specific control sites. The means by which the catalytic function of these enzymes is modulated by their interaction with specific low molecular weight ligands is being studied. These comparative studies with cariogenic and noncariogenic streptococci are designed to gain insight into a possible biochemical basis for pathogenicity and ultimately to formulate a rational approach for its control.

SPECIAL DESCRIPTORS: 0
NIDR CLASSIFICATION: 10140
TOTAL MAN YEARS : 1.50
PROFESSIONAL : 0.50
OTHER : 1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	C L Wittenberger	3/25/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBC401b62

NIDR-62B- 008

TITLE OF PROJECT

Cell Growth Studies in Normal and Abnormal Subjects

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: H. L. Cooper Chief, Cell Biology Section LB NIDR

OTHER: None

COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biochemistry
Section: Cell Biology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Biochemical processes which regulate the growth of human lymphocytes in vitro are being studied. The RNA metabolism of resting and growing lymphocytes is being investigated in order to clarify growth-related alterations in the synthesis, processing and degradation of various RNA species.

Messenger RNA will be isolated from lymphocytes by specific binding to polyadenylate sequences. Size distribution, kinetics of synthesis and degradation and movement among intracellular compartments will be studied. Differences between resting and growing lymphocytes for these characteristics will be sought.

Activity of appropriate fractions in cell free systems will be examined. These system include microinjection into öocytes and translation in the heterologous cell-free systems derived from wheat germ.

SPECIAL DESCRIPTORS: Blood
NIDR CLASSIFICATION: 41211
TOTAL MAN YEARS: 2.75
PROFESSIONAL: .75
OTHER: 2.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	H.L. Cooper /RS.	5/8/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBC201b62

NIDR-62B- 009

TITLE OF PROJECT

The Chemistry and Biosynthesis of Connective Tissue

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	G. R. Martin	Chief, Conn.Tissue S.	LB NIDR	R. Penttinen	Guest Worker	LB NIDR
OTHER:	P. Byers	Research Associate	LB NIDR	R. Orkin	Research Biol.	LB NIDR
	D. Rowe	Clinical Associate	LB NIDR	J. Ketley	Guest Worker	LB NIDR
	L. Wahl	Postdoctoral Fellow	LB NIDR	F. M. Pope	Guest Worker	LB NIDR
	T. Lustberg	Research Associate	LB NIDR	B. Smith	Res. Chemist	LB NIDR
	J. Lichtenstein	Guest Worker	LB NIDR			

COOP: Dept. of Medicine, Johns Hopkins Hospital, Baltimore, Md.

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biochemistry
Section : Connective Tissue
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The purpose of this project is to study the formation and destruction of connective tissue in normal and disease states. Particularly attention is directed toward collagen and elastin. Current active aspects of the project include the isolation and characterization of precursor forms, the study of inherited defects utilizing cells in culture and the examination of the mechanism through which connective tissue is altered by inflammation.

SPECIAL DESCRIPTORS: Blood Vessels, Lung
NIDR CLASSIFICATION: 20322
TOTAL MAN YEARS: 17.00
PROFESSIONAL: 11.00
OTHER: 6.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Geo. R. Martin	5/10/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBC102b62

NIDR-62B-010

TITLE OF PROJECT

The Chemistry of Collagen

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	K. A. Piez	Chief	LB NIDR
OTHER:	H. J. Evans	Staff Fellow	LB NIDR
	A. C. Nicholls	Visiting Fellow	LB NIDR
	G. Chandrakasan	Visiting Fellow	LB NIDR

COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biochemistry
Section: Protein Chemistry
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The broad aim of this project is to determine the covalent structure of collagen including both amino acid sequence and covalent interchain cross-links. Differences that can be related to tissue, species, developmental stage and connective tissue pathology are of particular interest. Currently active aspects of the study include the isolation and characterization of multichain peptides containing cross-links, the development of methods to scan small samples of collagen for differences, and the characterization of collagen from lower species of animals including ascaris cuticle collagen and codfish skin collagen.

SPECIAL DESCRIPTORS: Collagen Metabolism
NIDR CLASSIFICATION: 10210
TOTAL MAN YEARS: 8.75
PROFESSIONAL: 3.50
OTHER: 5.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	K. A. Piez	5/10/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-EPB003a63

NIDR-63A-011

TITLE OF PROJECT

Clinico-pathologic Studies of Human Oral Mucosa

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Archard, Howell O.	Dental Director	LOM	NIDR
OTHER:	None			
COOP:	National Cancer Institute, Laboratory of Pathology			
	National Cancer Institute, Dermatology Branch			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR/NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Human oral mucosal lesions of a keratotic nature are studied clinically and histologically over their duration for changes occurring in them. Lesions studied include hyperplastic, pre-malignant, and inherited mucosal disorders. Each case undergoes a detailed environmental analysis, appropriate laboratory studies are performed, and a record of the clinical and histologic changes is obtained in order to document the clinicopathologic progression of the disease.

Where indicated, appropriate correlative studies, such as histochemistry, electron microscopy, biodynamic (turnover) studies, immunofluorescent procedures, etc., are employed to provide additional significant data.

SPECIAL DESCRIPTORS:	Human
NIDR CLASSIFICATION:	33300
TOTAL MAN YEARS:	.50
PROFESSIONAL:	.50
OTHER:	.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	H. O. Archard	3/28/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBS206b63

NIDR-63B- 012

TITLE OF PROJECT

Infrared and Raman Spectroscopic Studies of Teeth and Bones and Related Synthetic Compounds

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Fowler, Bruce O.	Chemist	LBS	NIDR
COPI:	None			
OTHER:	None			
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The main objective is to determine compositional and structural details of the inorganic phase in teeth and bones. Infrared (4000-60 cm^{-1}) and Raman spectroscopy as well as chemical methods are employed in these studies. Methods are devised for preparation of synthetic calcium apatites of controlled physical properties (crystal size and perfection) and chemical composition containing biologically relevant constituents, e.g., hydroxyl, fluoride, chloride, carbonate, water and acid phosphate. The vibrational spectra of these apatites and related compounds are assigned and characterized. Isotopically enriched apatite analogs are prepared to facilitate spectral assignments. The spectroscopic assignments and supplemental spectral data (temperature dependency and polarization) are utilized to establish compositional and structural details of the apatites which include the type and geometry of ions, the site or number of sites occupied by ions, orientation of ions, chemical bonding and interactions of ions and semi-quantitative estimations of constituents present. The results of findings for the controlled apatite system are related to the inorganic phase in calcified tissues.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	10210
TOTAL MAN YEARS:	1.00
PROFESSIONAL:	1.00
OTHER:	None

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Bruce O. Fowler	27 March 1974

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBS401b63

NIDR-63A-013

TITLE OF PROJECT

Exogenous and Endogenous Factors Affecting Normal Development of the Oral Facial Region

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	King, Cecil T. G.	Research Physiologist	LBS	NIDR
OTHER:	Wilk, Ann L.	Research Chemist	LBS	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Experimental Pharmacology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Interspecies differences in the metabolism, placental transfer and fetal binding of the teratogens used are under investigation. In addition fetal outcome from prolonged versus acute drug administration is being studied to determine drug enzyme activation or the effects of drug-binding in the fetus. Special techniques are being used to determine drug effect on the developing mammalian embryo independent of the maternal metabolism and placental transfer.

SPECIAL DESCRIPTORS: Children
NIDR CLASSIFICATION: 41240
TOTAL MAN YEARS: 1.00
PROFESSIONAL: .50
OTHER: .50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Cecil T. King	3/25/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-HGB008a63

NIDR-63A- 014

TITLE OF PROJECT

Genetic Studies of Oral Diseases, Anomalies and Development

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Niswander, Jerry D.	Dental Director	Chief of HGB	HGB	NIDR
OTHER:	Chung, C. S.				(1)
COOP:	(1) School of Public Health, University of Hawaii				

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Human Genetics Branch
Section: Population Genetics
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Studies are being conducted on Hawaiian school children and among various Amerindian tribes in an attempt to clarify the relative role of genetic and environmental factors in certain oral conditions. These studies have as their objective: (a) to determine the effects of inbreeding and hybridization on malocclusion and dental caries; (b) to assess the role of environment in malocclusion--specifically has the frequency, type and severity of malocclusion changed over time, and if so, can the changes be related to socioeconomic status and changing cultural patterns; (c) to assess the correlation between relatives in malocclusion; and (d) to elucidate genetic mechanisms involved in morphological variations of the teeth.

SPECIAL DESCRIPTORS:	Human, Population Research
NIDR CLASSIFICATION:	44220
TOTAL MAN YEARS:	.75
PROFESSIONAL:	.25
OTHER:	.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Jerry D. Niswander

DATE: 3/25/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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Not for publication or publication reference.

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBS101b63

NIDR-63B-015

TITLE OF PROJECT

Experimentally Induced Enamel Defects

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Nylen, Marie U.	Chief, Lab. of Bio. Structure	LBS	NIDR
COPI:	None			
OTHER:	Larson, Rachel H.	Research Chemist	CP PR	NIDR
	Westergaard, Jytte			
COOP:	Royal Dental College, Copenhagen, Denmark			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Experimental Morphology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Previous studies have demonstrated that intraperitoneal injections of tetracycline hydrochloride to Sprague-Dawley rats can give rise to hypoplastic lesions in the enamel of any tooth that is under formation at the time of drug administration. The aim of the investigation this past year has been to define in detail the relationship of dose size, number of injections, concentration of drug and age of the experimental animal to serum levels of the antibiotic and incidence of enamel and dentin defects. In addition to these studies experiments have been initiated aimed at establishing the effect of sodium fluoride on molar formation in the Osborne-Mendel rat. One of the purposes of these studies is to establish model systems which can be used (1) to carry out in-depth studies into the cell changes which underlie development of tooth defects; (2) to follow pre- and post-eruptive changes in the enamel of hypoplastic teeth, and (3) to investigate the response of hypoplastic teeth to a cariogenic challenge.

SPECIAL DESCRIPTORS:	Children
NIDR CLASSIFICATION:	10300
TOTAL MAN YEARS:	2.35
PROFESSIONAL:	.75
OTHER:	1.60

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Marie U. Nylen	3/29/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBS431b63

NIDR-63A- 016

TITLE OF PROJECT

Norchlorcyclizine Teratogenesis; Alteration of Acid Mucopolysaccharides in Palatal Shelves and Cleft Palate Production in Rats

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Wilk, Ann L.	Research Chemist	LBS	NIDR
COPI:	King, C.T.G.	Research Physiologist	LBS	NIDR
OTHER:	Mazell, P.			(1)
COOP:	(1) Department of Pharmacology, George Washington University			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Biological Structure
Section: Experimental Pharmacology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Studies have shown that norchlorcyclizine alters acid mucopolysaccharide synthesis in palatal shelves of rat embryos prior to rotation. Investigations are being carried out on the mode of drug-macromolecule interactions, the nature of the resulting alteration and the effects on palatal development.

SPECIAL DESCRIPTORS: Children
NIDR CLASSIFICATION: 42220
TOTAL MAN YEARS: .80
PROFESSIONAL: .50
OTHER: .30

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Ann Louise Wilk	3/25/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-EPB001b64

NIDR-64B-017

TITLE OF PROJECT

Histochemical and chemical studies of normal and diseased tissues

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Gibson, William A.	Dental Director	LOM	NIDR
OTHER:	None			
COOP:	Spencer, Herta, Hines V.A. Hospital, Hines, Illinois			
	Bick, K.L., Georgetown University, Washington, D.C.			
	Dorey, C.K., Georgetwon University, Washington, D.C.			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Md., 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Histochemical and chemical studies carried out in normal and diseased tissues to determine the basic mechanisms involved in the pathogenesis of various oral diseases. Emphasis is placed on qualitative and quantitative changes in the various enzyme activities reflecting changes in basic metabolic activities. The periodontium of human and experimental animals, human oral mucosa in folic acid deficiency and polyoma induced salivary gland tumors in mice are currently being investigated.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	20325
TOTAL MAN YEARS:	3.00
PROFESSIONAL:	1.00
OTHER:	2.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	William A. Gibson	3/28/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. DIR203b65

NIDR-65B-018

TITLE OF PROJECT

The Response of Neurons in the Trigeminal Ganglion and Trigeminal Brain-stem Nucleus

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Dubner, Ronald	Dent Dir, Ch Neur Mech Sect	CD NA	NIDR
COPI:	Beitel, Ralph E.	Staff Fellow	CD NA	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Neurobiology and Anesthesiology Branch
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Microelectrode recordings from the trigeminal ganglion and from the rostral and caudal divisions of the trigeminal brain-stem nuclei are performed in anesthetized monkeys. Mechanical, thermal, and noxious stimuli are applied to the face and oral mucosa and the response properties of single neurons are recorded and stored on magnetic tape. Data is analyzed with the aid of an on-line, real-time computer system.

SPECIAL DESCRIPTORS:	NONE
NIDR CLASSIFICATION:	60210
TOTAL MAN YEARS:	1.25
PROFESSIONAL	.75
OTHER:	.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Ronald Dubner

DATE: 3/28/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-EPB004a66

NIDR-66A- 019

TITLE OF PROJECT

Clinical and Morphologic Studies of the Human Dentition in Acquired and Inherited Metabolic Diseases

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Archard, Howell O. Dental Director LOM NIDR

OTHER: None

COOP: National Heart and Lung Institute, Endocrinology Branch
National Institute of Arthritis and Metabolic Diseases, Metabolic Diseases Branch
National Institute of Neurological Diseases and Strokes, Section on Child Neurology

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Clinical and morphologic characteristics of the deciduous and permanent teeth of individuals affected with a wide variety of inherited or acquired metabolic diseases are studied. The gross and microscopic changes in the teeth are recorded, and correlations with the developmental events and general metabolic changes are undertaken.

Teeth removed from patients with metabolic disease who have been studied at the Clinical Center of the National Institutes of Health, comprise the major source of material, although specimens from outside sources are studied as well. Disorders currently under study include: Hereditary hypophosphatemia (Vitamin D-resistant rickets), hypophosphatasia, pseudohypoparathyroidism, pseudo-pseudohypoparathyroidism, Hurler's syndrome, diabetes, insipidus, ectodermal dysplasia, chronic Vitamin D intoxication, infantile hypercalcemia, primary hyperoxaluria, porphyria, the Fanconi syndrome, cystinuria, acatalasia, etc.

SPECIAL DESCRIPTORS: Human and Children
NIDR CLASSIFICATION: 10210
TOTAL MAN YEARS: .50
PROFESSIONAL: .50
OTHER: .00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	H. O. Archard	3/28/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. DIR201b66 NIDR-66B-020

TITLE OF PROJECT

Anatomical Studies of the Organization of the Main Sensory and Spinal V Nuclei

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Gobel, Stephen	Sr Dental Surgeon	CD NA	NIDR
COPI:	Purvis, Marlene B.	Biol Lab Tech -Animal-	CD NA	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Neurobiology and Anesthesiology Branch
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This project involves light and electron microscopical studies of the neuronal morphology and organization of the neuropil of the main sensory and spinal V nuclei in rats, cats and monkeys. The objectives of these studies are to broaden our understanding of oral-facial sensation and the mechanisms of pain.

SPECIAL DESCRIPTORS: NONE
NIDR CLASSIFICATION: 60210
TOTAL MAN YEARS: 2.0
PROFESSIONAL 1.0
OTHER: 1.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Stephen Gobel

DATE: 3/28/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. EPB006c66

NIDR-66C- 021

TITLE OF PROJECT

Oncological Research

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Hamner III, James E.	Dental Director	LOM	NIDR
OTHER:	None			
COOP:	Pindborg, Jens J., The Royal Dental College, Copenhagen, Denmark			
	Mehta, Fali S., Tata Institute Fundamental Research, Bombay, India			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Scientific investigations underway or planned for the immediate future include: a) continued accumulation of fibro-osseous study cases; b) continued 10 year follow-up of oral cancer and oral premalignant conditions in 65,000 rural Indian villagers with Dr. Mehta and Dr. Pindborg; c) collaboration as a Collecting Center for oral precancerous conditions with other World Health Organization designated centers; and d) clinical and basic studies of fibro-osseous lesion and oral carcinoma cases within the Clinical Center framework. Basic investigations of the carcinogenic potential of the ingredients of betel quid are being conducted on baboons (Papio cynocephalus) under contract arrangement with the Southwest Foundation for Research & Education in San Antonio, Texas by Dr. Hamner.

SPECIAL DESCRIPTORS:

NIDR CLASSIFICATION:	33200
TOTAL MAN YEARS:	1.00
PROFESSIONAL:	1.00
OTHER:	.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	James E. Hamner III	4/11/69

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LMI010b66

NIDR-66B-022

TITLE OF PROJECT

Phytogenetic Mapping of Lactic Acid Bacteria and Related Microorganisms

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	London, Jack	Research Microbiologist	LMI	NIDR
OTHER:	Chase, Nina	Chemist	LMI	NIDR
	Kline, Kimberly	Microbiologist	LMI	NIDR
	Neimark, Harold			
COOP:	State University of New York			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section : Microbial Physiology
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – 200 words or less – Omit Confidential data.)

Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in these areas and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Fructose diphosphate aldolase has been used as an evolutionary marker to trace the phylogenetic relationships among members of the lactic acid bacteria. Thus far, two reference points have been employed in these studies. Antisera prepared against the pure FDP aldolases of Streptococcus faecalis MR and Pediococcus cerevisiae were used to detect structural relatedness among aldolases from organisms belonging to seven genera. The present phylogenetic map encompasses the following genera: Streptococcus, Lactobacillus, Pediococcus, Aerococcus, Butyribacterium, Eubacterium and Propionibacterium. It appears that these morphologically diverse forms have been derived from a common ancestor. In addition to establishing the degree of relatedness between the various species, these techniques have also been used to ascertain the validity of speciation determined by classical taxonomic methods. Those strains belonging to legitimate species tend to cluster together at a single locus on the map while strains belonging to poorly defined species do not cluster and map at more than one locus.

NIDR CLASSIFICATION: 10110
TOTAL MAN YEARS : 1.75
PROFESSIONAL : 1.00
OTHER : .75

PROFESSIONAL SCHOOL (medical, dental, etc.) WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	[signature]	7/25/74

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SUPPORTING AGENCY

METHOD OF SUPPORT (Check one)

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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Not for publication or publication reference.

U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LMI014b66

NIDR-66B-023

TITLE OF PROJECT

Systematic Microbiological Taxonomic Studies

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Rogosa, Morrison	Research Microbiologist	LMI	NIDR
OTHER:	Krichevsky, Micah	Research Chemist	ODIR	NIDR
	Colwell, Rita			(1)
	Gherna, Robert			(2)
	Mills, Charles			(2)

COOP: (1) University of Maryland
(2) American Type Culture Collection

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section : Microbial Physiology
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Integrated studies will be continued on common reactions, utilization of substrates and metabolic pathways in the lactic acid bacteria representing chiefly Lactobacillus, Leuconostoc, and Pediococcus. New differential tests and comparative enzyme functions in the lactic acid bacteria will be studied further. The definition of the term "lactobacilli and related organisms" is being expounded. Computer storage and information programming of microbial characteristics will continue.

NIDR CLASSIFICATION: 10110
TOTAL MAN YEARS : 1.50
PROFESSIONAL : 1.00
OTHER : 50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	E. L. Wittenberger	3/28/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-HGB003b67

NIDR-67B- 024

TITLE OF PROJECT

Developmental Processes in Genetically Controlled Malformations

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Brown, Kenneth S.	Medical Director	HGB	
OTHER:	Johnston, Malcolm C.	Visiting Scientist	HGB	
	Leyshon, Webster C.	Biologist	HGB	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Human Genetics Branch
Section: Developmental Genetics
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK

The objectives of this project are to describe the development of experimental animals with genetically produced congenital malformations, particularly those of the oral region, and to examine the interaction between the tissues of these animals in the developmental processes in order to determine the nature of the mechanism producing the genetic defect.

Several methods will be employed. A survey of mouse mutants is being undertaken to evaluate their oral structures in relation to those of the lines from which they arose. Mutants of specific interest are being collected, and colonies of these animals are to be developed as a basis for experimental study. Timed matings are being made to produce animals of known gestational age. Serial sacrifice and histological study will produce systematic documentation of the developmental processes. Comparative differences in rate of cleft palate and cleft lip and palate in inbred strains of mice are being studied as a response to changes in maternal environment during different stages of pregnancy.

Assays of hormonal levels during pregnancy and during teratogenic stimulation are being carried out to evaluate the effects of hormones on development of defects.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	41230
TOTAL MAN YEARS:	7.00
PROFESSIONAL:	2.75
OTHER:	4.25

PROFESSIONAL SCHOOL (medical, dental, etc.) WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Kenneth S. Brown

DATE: 3/25/74

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SUPPORTING AGENCY

METHOD OF SUPPORT (Check one)

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBC402b67

NIDR-67B-025

TITLE OF PROJECT

In Vitro Synthesis of Collagen and Characterization of the Messenger RNA for Collagen

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Dr. R. Stern	Acting Chief, Cell Biology S.	LB	NIDR
OTHER:	Dr. Kathy Benveniste	Staff Fellow	LB	NIDR

COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biochemistry
Section: Cell Biology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

It is the purpose of this study to synthesize procollagen in cell-free protein synthesizing systems derived from heterologous sources, from animal cells (Krebs II mouse ascites tumor) and from a plant extract (wheat germ). Collagen messenger RNA from chick embryo calvaria (Type I collagen) and mouse chondrosarcoma (Type II collagen) are being examined. This study is divided into several portions.

1. Comparison of ribosomes from various sources in their ability to support collagen synthesis
2. Search for and fractionation of collagenous tissue specific tRNAs, particularly tRNAs for glycine and proline.
3. Examination of protein synthesizing factors such as collagenous tissue specific initiation factors and their role in translational control of collagen synthesis.
4. Evaluation of the cell-free synthetic collagenous product.
5. Purification and characterization of the collagen specific messenger RNA as to size, base composition and oligonucleotide fingerprint pattern following nuclease digestion.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 41211
TOTAL MAN YEARS: 3.0
PROFESSIONAL: 2.0
OTHER: 1.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Robert Stern	5/8/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-OMS007c68

NIDR-68C-026

TITLE OF PROJECT

Cryoglobulins in Oral Stomatitis and Connective Tissue Disease

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Norman A. Cummings	Medical Officer	LOM	NIDR
COPI:	None			
OTHER:	None			
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

An investigation of the incidence and severity of cryoglobulinemia in Behcet's syndrome, aphthous stomatitis and other connective tissue disease will be done. Subtypes of globulins and possible cryo-antibody activity will also be explored.

SPECIAL DESCRIPTORS:	Humans
NIDR CLASSIFICATION:	32000
TOTAL MAN YEARS:	.50
PROFESSIONAL:	.25
OTHER:	.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Thomas A. Cummings, M.D.	3/29/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Grant ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-OMS009c68

NIDR-68C-027

TITLE OF PROJECT

Study of Behcet's Syndrome and Aphthous Stomatitis

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Norman A. Cummings	Medical Officer	LOM	NIDR
COPI:	None			
OTHER:	Edward A. Graykowski	Medical Director	LOM	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Patients with Behcet's syndrome will be studied with regard to the natural history of their clinical course. Their immunologic response to various antigens, the incidence and extent of neurologic involvement, and the response to various therapeutic modalities will also be assessed. Comparison to patients with aphthous stomatitis will also be made, and an evaluation of possible viral etiology carried out.

SPECIAL DESCRIPTORS:	Clinical Trials; Human
NIDR CLASSIFICATION:	32400
TOTAL MAN YEARS:	.50
PROFESSIONAL:	.25
OTHER:	.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Norman A. Cummings, MD	3/29/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBS111b68

NIDR-68B-028

TITLE OF PROJECT

Ultrastructure and Cytochemistry of Salivary Glands

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Hand, Arthur R. Senior Dental Surgeon LBS NIDR
COPI: None
OTHER: Hamosh, Margit
COOP: Laboratory of Nutrition and Endocrinology, National Institute of Arthritis, Metabolism, and Digestive Diseases

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Experimental Morphology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The ultrastructure and cytochemistry of the rat parotid gland are being studied. Emphasis is placed upon the basic mechanisms involved in exocrine secretion, with particular attention directed to the role of the Golgi apparatus and lysosomes in these phenomena. Other exocrine glands, including the pancreas and lacrimal gland, are also being examined in order to make comparisons with the parotid gland and to take advantage of cytochemical characteristics particularly suited for study by electron microscopy.

The biochemistry, ultrastructure, and cytochemistry of developing and adult von Ebner's glands are also being studied, in order to determine the localization of secretory enzymes, particularly lipase, and the development of the secretory capabilities of the serous cells of the rat tongue.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 34200
TOTAL MAN YEARS: 2.10
PROFESSIONAL: .80
OTHER: 1.30

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Arthur R Hand	3/29/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DA

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. CPR002A68

NIDR-68C -029

TITLE OF PROJECT

The effect of school water fluoridation on dental caries

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Heifetz, Stanley B.	Dental Director	CPPR	NIDR
COPI:	Horowitz, Herschel S.	Dental Director	CPPR	NIDR
OTHER:	Law, Frank E.	Consultant	OD	NIDR
COOP:	Division of Water Hygiene, Environmental Protection Agency, and Dental Health Division, North Carolina State Board of Health			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section : Community Programs
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK - *(200 words or less — Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

In 1968, fluorides were added to the well water supply of a consolidated school (grades 1-12) in Seagrove, North Carolina at 6.3 ppm, seven times the optimal level recommended for community fluoridation in the geographic area. Children attending the Seagrove School live in an area without a central water supply and where the various drinking waters contain negligible levels of fluoride. Children are exposed to the higher concentration of fluoride at school in an attempt to duplicate the total fluoride intake of children who drink optimally fluoridated water on a full-time basis. Prior to the installation of fluoridation equipment, dental examinations using the DMF surface index were conducted on approximately 1100 children to determine base line caries prevalence. Four-year, follow-up examinations were conducted in May 1972. A brief report containing the four-year findings was presented at the 1973 IADR meeting and the full paper was published in the February 1974 issue of JADA. Follow-up examinations will continue to be conducted at four-year intervals to measure caries-protective benefits as increasingly larger segments of the study population become continuously exposed to fluoridated water at school since entering the first grade. On the eight-year follow-up examinations, an assessment of the prevalence of fluorosis, if any, will be made along with the regular examinations for dental caries.

SPECIAL DESCRIPTORS: Human, Clinical Trials, Children, Water
NIDR CLASSIFICATION: 10550
TOTAL MAN YEARS: .5
PROFESSIONAL: .25
OTHER: .25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Stanley B. Heifetz	4/19/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. DIR001a68

NIDR-68A-030

TITLE OF PROJECT

Laboratory Automation

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Medlin, Terry P.	Head, Scientific Unit	OD	NIDR
COPI:	Robinson, Merle S.	Computer Programmer	OD	NIDR
	Wilson, John J.	Chief, Data Process&Analysis	OD	NIDR
COOP:	Computer Systems Laboratory, Division of Computer Research and Technology, NIH			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office, Office of the Director
Section: Data Processing Systems & Analysis
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This project is a joint collaborative endeavor on the part of NIDR and of the Division of Computer Research and Technology, NIH.

It is a laboratory automation project which is involved in the concurrent on-line acquisition and real time processing of data from a number of analytical instruments and experiments. The project also involves the control of bacteria growth experiments. The computer complex (Honeywell H-316 and H-516) operates under the OLERT multi-programming operating system. The system is interfaced with an amino acid analyzer, liquid scintillation counters, a spectrophotometer, a gas chromatograph, X-ray diffractometer, a fermenter-pumping system and neurophysiology microelectrode experiments. Telecommunication with the NIH central IBM 370 and PDP-10 computers has been established. Extensions of the system to include more of these devices are being considered and will necessitate hardware expansion. In particular 2 more scintillation counters, one more X-ray diffractometer, 2 more spectrophotometers, and one new gas chromatograph are currently be integrated as well as a second neurophysiological laboratory for behavioral studies.

SPECIAL DESCRIPTORS:	NONE
NIDR CLASSIFICATION:	10290
TOTAL MAN YEARS:	4.25
PROFESSIONAL	1.00
OTHER	3.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Terry P. Medlin	

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. DIR204a69

NIDR-69A-031

TITLE OF PROJECT

Computer Interfacing of Neurophysiologic and Laboratory Instrumentation

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Brown, Frederick J. Electronic Engineer (Instru) CD NA NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Neurobiology and Anesthesiology Branch
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This work involves the development of suitable electronic and electromechanical instrumentation to be used in neuro-physiological and behavioral research. It involves the adaptation and interfacing of these and other instruments to a multipurpose computer installation.

SPECIAL DESCRIPTORS: NONE
NIDR CLASSIFICATION: 60240
TOTAL MAN YEARS: 1.0
PROFESSIONAL 1.0
OTHER: .0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Frederick J. Brown

DATE: 3-28-74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Ser. No. CPR-003A69

NIDR-69 A-032

TITLE OF PROJECT

Effects of acidulated phosphate-fluoride chewable tablets on dental caries in school childre

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Driscoll, William S.	Sr. Dent. Surg.	CP PRNIDR	NIDR
OTHER:	Heifetz, Stanley B.	Dental Director	CP PR	NIDR
	Korts, David C.	Staff Fellow	CP PR	NIDR
	Horowitz, Herschel S.	Dent Dir, Chief,CPS	CP PR	NIDR
COOP:	Dental Health Division, North Carolina State Board of Health and the Public Schools of Wayne County, North Carolina			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section : Community Programs
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK - *(200 words or less — Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Baseline dental examinations were conducted in September 1969 on approximately 1000 first- and second-grade school children in Wayne County, North Carolina. Children assigned to one test group chew an acidulated phosphate-fluoride (APF) tablet containing 1 mg. F., rinse for 30 seconds with the resulting solution and then swallow the material. Another test group follows the same procedure but, in addition, they repeat the procedure at least 3 hours later with another APF tablet, also containing 1 mg. F. A third group uses a placebo tablet and serves as a control. The treatments are carried out each day in school under supervision of the classroom teacher. Treatments will continue until the participants have completed the eighth grade. The first follow-up evaluation was conducted in April 1972, after 30 months of study. A brief report of the 30-month findings was presented at the 1973 IADR meeting and the manuscript has been accepted for publication in the JADA. The second follow-up examination will be carried out in May 1974 (after 55 months of study). On the 1974 examinations, in addition to the regular caries assessment, a 50 percent sample of the participants will be examined for possible dental fluorosis. Future follow-up examinations will be conducted at 2-3 year intervals.

SPECIAL DESCRIPTORS:	Human, Clinical Trials, Children
NIDR CLASSIFICATION:	10540
TOTAL MAN YEARS:	1.25
PROFESSIONAL:	1.0
OTHER:	.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	William S. Driscoll	4/18/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBS320b69

NIDR-69B- 033

TITLE OF PROJECT

Studies on Oral Filamentous Microorganisms Implicated in Periodontal Disease

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Hageage, George J.	Research Microbiologist	LBS	NIDR
COPI:	Bladen, Howard A.	Research Microbiologist	LBS	NIDR
OTHER:	Thompson, L. Ariel	Sr. Dental Surgeon	CP PR	NIDR
	Keyes, Paul H.	Dental Director	CD CI	NIDR
	Tanzer, Jason M.			
COOP:	University of Connecticut Health Center, Farmington, Conn.			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Structural Interactions
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The general objectives of this project involve the structure, taxonomy, epidemiology, immunology and pathogenicity of gram-positive oral filamentous bacteria of rodent and human origin implicated in the initiation of periodontal pathosis. Present studies involve (1) the development and application of (a) fluorescent antibody technique and (b) solid phase microradioimmunoassay for the detection and rapid identification of these microorganisms in plaque and (2) the isolation and characterization of antigens which may play a role in the initiation of inflammation.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	20211
TOTAL MAN YEARS:	3.00
PROFESSIONAL:	1.00
OTHER:	2.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	George J. Hageage	3/27/74

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LMI 003669

NIDR-69B-034

TITLE OF PROJECT

Immunological Mechanisms Involved in Histamine Liberation

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Hook, William A.	Research Microbiologist	LMI	NIDR
COPI:	Siraganian, Reuben P.	Medical Officer Research	LMI	NIDR
OTHER:	Washington, Julian H.	Biological Lab. Tech. Animal	LMI	NIDR
COOP:	NONE			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Microbiology and Immunology
Section: Clinical Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Histamine release from mast cells and blood basophils of several different species is studied as one of the immunological mechanisms involved in inflammation. The molecular size and nature of the antigenic determinants required to activate the cell for histamine release has been studied. The interaction of different antigens in their reaction at the basophil surface is being evaluated. The role of serum factors including complement in the liberation of histamine from human basophils is also being studied.

SPECIAL DESCRIPTORS: Human Blood
NIDR CLASSIFICATION: 20315
TOTAL MAN YEARS: 2.40
PROFESSIONAL: 1.40
OTHER: 1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: William A. Hook

DATE: 3/29/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Contract ☐ Research Contract ☐ Research Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LMI004b69

NIDR-69B -035

TITLE OF PROJECT

Activation of B and T Lymphocytes to Produce Lymphokines and Proliferate

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Oppenheim, Joost J.	Medical Officer - Research	LMI	NIDR
OTHER:	Rosenstreich, David	Senior Staff Fellow	LMI	NIDR
	Dougherty, Suanne F.	Biologist	LMI	NIDR
	Altman, Leonard C.	Surgeon	LMI	NIDR
	Mackler, Bruce			
COOP:	Litton Bionetics			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section : Cellular Immunology
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The reactions of purified B and T cells to mitogens and antigens are being investigated. T cells from agammaglobulinemic chickens proliferate in response to mitogens and produce chemotactic factor. However, in humans both purified T and B cells were found to proliferate in response to appropriate stimulants and make chemotactic factors. These findings have been applied to study patients with periodontal disease. Their T as well as B cells have been found to proliferate and make mediators when stimulated by plaque antigens. These observations suggest a redefinition of the role of B cells in inflammation is required and needs further study.

NIDR CLASSIFICATION: 20220
TOTAL MAN YEARS : 1.00
PROFESSIONAL : .75
OTHER : .25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Joost J Oppenheim	3/28/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBS202b70

NIDR-70B-036

TITLE OF PROJECT

X-ray Diffraction Study of Lamellar Lecithin Mesophases

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Eanes, Edward D. Chief, Molecular Structure Section LBS NIDR
COPI: None
OTHER: Gottlieb, Melvin H.
COOP: Laboratory of Physical Biology, National Institute of Arthritis and Metabolic Diseases

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The effect of added electrolytes on the thickness of phospholipid bilayers in lecithin-water mixtures is being investigated by small-angle x-ray diffraction techniques. Electrolytes being investigated are LiCl, NaCl, Na_2SO_4, CsCl, KCl, $CaCl_2$, and HCl. The effect of electrolytes on the maximal amount of solution that can be mixed with lecithin before phase separation occurs is also being determined.

X-ray diffraction examination of red blood cell membrane preparations is also currently being conducted.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 20220
TOTAL MAN YEARS: .40
PROFESSIONAL: .20
OTHER: .20

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Edward D. Eanes	3/29/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DA

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. CPR001a70

NIDR-70C-037

TITLE OF PROJECT

The efficacy of an adhesive resin in preventing occlusal caries

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Horowitz, Herschel S.	Dent Dir, Chief,CPS	CP PR	NIDR
OTHER:	Heifetz, Stanley B.	Dental Director	CP PR	NIDR
	Poulsen, Sven	Guest Worker	CP PR	NIDR
COOP:	Dental Division of the Montana State Health Department			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Community Programs
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

In May 1970, baseline dental examinations were conducted on 700 grade school children in kindergarten and grades 1, 6 and 7, in Kalispell, Montana, a non-fluoridated community. A total of 450 children were found to have one or more sound pairs of homologous permanent teeth. Only these children were included in the study. One-half of the mouth of each subject was randomly designated as the test side and the other half served as the control side. On the test side, sound occlusal surfaces were conditioned and sealed with the Bis-GMA sealant material developed by Buonocore. Teeth were cleaned in preparation for the sealant by a dental hygienist. Public Health Service dentists did the actual conditioning and application. The physical properties of the sealant including the extent of loss has been evaluated at five, nine, 12, 24 and 36 months after application. Follow-up examinations for dental caries increment have been made after one, two and three years of study. Two-year findings will be presented at the 1974 meeting of IADR and have been submitted to JADA for publication. Three-year findings are currently being processed. Long-term, follow-up examinations of the sealant are needed to obtain information on the duration of the sealant's retentiveness and the caries susceptibility of pits and fissures from which sealant has been lost (totally or partly). Therefore, 4-year follow-up examinations have been scheduled for April 1974.

SPECIAL DESCRIPTORS: Human, Clinical Trials, Children
NIDR CLASSIFICATION: 10530
TOTAL MAN YEARS .5
PROFESSIONAL: .25
OTHER: .25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Herschel S. Horowitz	4/18/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 6-72

NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-HGB004b70

NIDR-70B-038

TITLE OF PROJECT

Embryological Studies of Facial Development

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Johnston, Malcolm C.	Visiting Scientist	HGB	NIDR
OTHER:	Bhakdinaronk, Anonknart	Visiting Fellow	HGB	NIDR
	Continued on separate sheet			
COOP:	(1) Hospital for Sick Children, Toronto			
	(2) University of Massachusetts			
	(3) American Dental Association			
	(4) University of North Carolina			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Human Genetics Branch
Section: Developmental Genetics
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are to study the migrations, interactions and derivatives of neural crest and other primordia involved in normal embryological facial development and to use the information for the study of facial malformations. The normal aspects of the study are conducted primarily on avian and rodent embryos, the latter developing in organ culture. Various histological and biochemical techniques are used. These include radioautography (and other procedures for following the migrations of cells) histochemistry, and column chromatography, as well as fluorescence, interference contrast and electron microscopy. The embryogenesis of spontaneous and induced malformations, particularly cleft lip and palate, is being studied in the mouse. Efforts are being made to influence the abnormal processes leading to "spontaneous" clefts through manipulation of environmental factors.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	41230
TOTAL MAN YEARS:	4.75
PROFESSIONAL:	2.50
OTHER:	2.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	M. C. Johnston	3/25/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DA

PHS-166
REV. 5-70

OTHER: Continued

Larson, Mary Alice	Biological Lab. Tech.-Micro.	HGB	NIDR
Brown, Kenneth S.	Medical Director	HGB	NIDR
Pratt, Robert M. Jr.	Sr. Staff Fellow	LBS	NIDR
Hassell, John R.	Staff Fellow	LBS	NIDR
Hazelton, R. D.			(1)
Noden, D. M.			(2)
Steffek, A. J.			(3)
Peach, R.			(4)

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-CPR22b70

NIDR-70A -039

TITLE OF PROJECT

Study of the mode of action of ambient fluoride on the development of dental caries

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Larson, Rachel H.	Research Chemist	CP PR	NIDR
OTHER:	Mellberg, James R.			(1)
COOP:	(1) The Kendall Company, Barrington, Illinois			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Preventive Methods Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The ultimate goal of this work is to determine the minimum fluoride exposure associated with maximum caries protection in humans. The rat is being used as the animal model for studying the mode of action of ambient fluoride, which will be provided by a number of experimental procedures.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10550
TOTAL MAN YEARS: 1.5
PROFESSIONAL: 0.5
OTHER: 1.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Rachel H. Larson	April 19, 197

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

NIH - 1946 (FORMERLY PHS - 166)
REV. 6-72

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. DIR202b70

NIDR-70B-040

TITLE OF PROJECT

Activity of Trigeminal Afferent Fibers of the Monkey in Response to Noxious and Innocuous Stimuli

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Sumino, Rhyuji	Visiting Associate	CD NA	NIDR
COPI:	Dubner, Ronald	Dent Dir, Ch Neur Mech Sect	CD NA	NIDR
	Starkman, Sidney	Research Associate	CD NA	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Neurobiology and Anesthesiology Branch
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Under barbiturate anesthesia, thin nerve bundles are dissected from the infraorbital and inferior alveolar nerves, and their electrical activity recorded and stored on magnetic tape. Thermal and noxious heat stimuli are delivered with a precisely-controlled thermode which has a temperature range of 20°C to 60°C and can produce a temperature change of 20°C at the thermode-skin junction within one second. Data is analyzed with the aid of an on-line, real-time computer system.

SPECIAL DESCRIPTORS: NONE
NIDR CLASSIFICATION: 60210
TOTAL MAN YEARS: 1.25
PROFESSIONAL 1.00
OTHER: .25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	R. Sumino	March 28 '74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LMI008b71

NIDR-71B-041

TITLE OF PROJECT

Chemotactic Factors and their Role in Human Diseases

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Altman, Leonard C	Surgeon	LMI	NIDR
OTHER:	Kennedy, John	Biologist	LMI	NIDR
	Blaese, Michael			
COOP :	National Cancer Institute, NIH, Bethesda, Maryland			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section : Humoral Immunity
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Work presently underway or planned, involves the study of lymphokine chemotactic factor synthesis in Wiskott-Aldrich syndrome, Hodgkin's disease, non-Hodgkin's lymphoma, malaria and other infectious neoplastic and immunodeficiency diseases. In addition, the migration of mononuclear leukocytes from patients with these diseases is being studied.

Secondly, the mechanism of activation of human B and T lymphocytes, their role in producing biologically-active lymphokines, and a comparison of physiochemical properties of the chemotactic lymphokines produced by T and B lymphocytes is under investigation.

SPECIAL DESCRIPTORS: Human
NIDR CLASSIFICATION: 20312
TOTAL MAN YEARS : 2.00
PROFESSIONAL : 1.00
OTHER : 1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Leonard C. Altman M.D	3/27/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. DIR106b71

NIDR-71B-042

TITLE OF PROJECT

Sucrose Metabolism by Streptococcus Mutans

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Chassy Bruce M.	Research Chemist	ODIR	NIDR
COPI;	Palumbo, Emily Victoria	Chemist	ODIR	NIDR
	Krichevsky, Micah I.	Chief, Environmental Mech. Sect.	ODIR	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Environmental Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The utilization of sucrose by Streptococcus mutans is an integral part of the formation of carious lesions on the smooth surfaces of the teeth. In order to understand this process it is necessary to study the sucrases, or sucrose utilizing enzymes, biochemically and physiologically. This study has isolated and characterized extracellular invertase as well as dextran sucrase and levan sucrase from the five serotypes of S. mutans, as well as from other oral streptococci. Further purification and characterization is in progress. Comparative studies are anticipated, especially with respect to determining immunological simmilitude. Results so far suggest that S. mutans is a heterogeneous species; this fact warns against generalizations concerning the mechanism of carious lesion formation until more basic knowledge is available.

The products of sucrase activity (i.e., dextran and levan) are uncharacterized as well. An effort is now in progress to do structural determinations on the products of individual isolated sucrases. These studies may be extended to plaque polysaccharides, especially those presently uninvestigated such as polysaccharides from actinomycetes.

SPECIAL DESCRIPTORS:	NONE
NIDR CLASSIFICATION:	10280
TOTAL MAN YEARS:	2.25
PROFESSIONAL	1.75
OTHER	.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	I. Bruce M. Chassy	4/15/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR=71B-043

Prev. Ser. No. DIR105b71

TITLE OF PROJECT

Extracellular Polysaccharide Formation by Streptococcus Mutans

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Donkersloot, Jacob A.	Staff Fellow	ODIR	NIDR
COPI:	Chassy, Bruce M.	Research Chemist	ODIR	NIDR
	DeLeon, Hector A.	Visiting Fellow	ODIR	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Environmental Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Streptococcus mutans and sucrose have been implicated in the etiology of smooth surface caries. The formation of polysaccharide from sucrose by S. mutans is believed to be of major importance in this disease process. Both fructan and glucan type polysaccharides can be formed, but in the particular strain used in this study (SL-1), only glucan formation is important. This reaction is catalyzed by dextransucrase (glucosyltransferase). We have found several such activities in extracellular fluids by isoelectric focussing and electrophoresis in gels. The products made by these isolated enzymes are either water-soluble or insoluble. To understand the relationship between these enzymes and their relevance in caries etiology, a search for mutants deficient in these activities was initiated. Several mutants were isolated, but so far only one has been studied in detail. This 15-3 mutant forms much more water-soluble and less insoluble glucan than the parent. New enzyme assays were developed to quantify these observations. Also, the mutant adheres less to surfaces in the presence of sucrose. These results suggest that soluble glucan acts as a precursor for the insoluble glucan in the parent strain. In the mutant, this latter reaction appears to be blocked. Presently, we are investigating the chemical nature of the soluble and insoluble glucan polymers.

SPECIAL DESCRIPTORS:	NONE
NIDR CLASSIFICATION:	10240
TOTAL MAN YEARS:	3.50
PROFESSIONAL	3.25
OTHER	.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Jacob A Donkersloot	4/15/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION D

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. DIR108a71

NIDR-71A-044

TITLE OF PROJECT

Handling of Microbial Strain Information by Computers

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Krichevsky, Micah I.	Chief, Environmental Mech. Sect.	ODIR	NIDR
OTHER:	Rogosa, Morrison	Research Microbiologist	LMI	NIDR
	Norton, L.			(1)
	Colwell, R. R.			(2)
	Skerman, V.B.D.			(3)
	Socransky, S. S.			(4)
	Lapage, S. P.			(5)

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Environmental Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Definition and standardization of the questions that are asked about microbial strains in a computer-compatible form is the first goal. Programs are being developed to enter data and retrieve it in a variety of ways for epidemiological, diagnostic, taxanomic, ecological, etc. uses. The long term goal is to establish a world-wide data bank at a series of cooperating centers.

A data file of primary data on a large number of bacteria found in the oral cavity and related types is being established. This file will provide a resource for asking both ecological and epidemiological questions of interest in dental research.

Findings from these efforts have already demonstrated that new classification methods are needed for oral filimentous bacteria. The classical taxanomic codes do not apply. Further, computer comparisons of large volumes of data have allowed design of rational antibiotic therapy for periodontosis as well as design of selective media.

SPECIAL DESCRIPTORS: NONE
NIDR CLASSIFICATION: 10250
TOTAL MAN YEARS: 1.75
PROFESSIONAL .25
OTHER 1.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Micah I. Krichevsky

DATE: 4/15/74

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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COOP:
(1) Division of Computer Research and Technology, NIH
(2) Biology Department, Georgetown University, American Type Culture Collection
(3) University of Queensland, Brisbane, Australia
(4) Forsyth Dental Center, Boston, Massachusetts
(5) Central Public Health Laboratory, London

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-71C-045

Prev. Ser. No. NIDR-LMI002c71

TITLE OF PROJECT

Contribution of Macrophages to Activation of T and B Lymphocytes and Production of Bone Resorbing Factor

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Oppenheim, Joost J.	Medical Officer - Research	LMI	NIDR
OTHER:	Rosenstreich, David	Senior Staff Fellow	LMI	NIDR
	Mergenhagen, Stephan E.	Chief, Lab of Micro. and Immunol.	LMI	NIDR
	Dougherty, Suanne F.	Biologist	LMI	NIDR
	Weedon, Lynda L.	Biologist	LMI	NIDR
	Wahl, Sharon M.	Staff Fellow	LMI	NIDR

(1)Horton, John E., (2) Raisz, L.

COOP: (1)Walter Reed Army Institute of Research, (2) University of Rochester Med. School

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section : Cellular Immunology
Location : NIDR,NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The interaction of macrophages with lymphocytes is a prerequisite for antigen-induced stimulation of in vitro lymphocyte proliferation and the production of a variety of mediators such as osteoclast activation factor (OAF) which results in bone resorption. This principle was tested to determine the nature of the OAF producing cells. OAF was found to be produced by lymphocytes, provided macrophages were there to activate them to make it. Furthermore, "OAF-like" activity was also found in the supernatants of long-term "B" lymphoid cell lines.

We have therefore also studied which class of lymphocytes (B or T) macrophages interact with. Macrophages were found to restore the response of purified T but not B lymphocytes, whereas the reaction of both T and B lymphocytes was enhanced in lymphocyte suspensions containing both B and T cells. Therefore, macrophages appear to facilitate the cooperation of T and B cells, but do so by interacting only with T cells. The differences in interaction of T and B receptors with stimulants suggested by these findings are being studied further.

NIDR CLASSIFICATION: 20314
TOTAL MAN YEARS : 1.50
PROFESSIONAL : 1.00
OTHER : .50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Joost J. Oppenheim	3/26/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LMI008b71

NIDR-71B-046

TITLE OF PROJECT

Production of Chemotactic Factors by Guinea Pig B and T Lymphocytes and Their Role in Acute and Chronic Inflammatory Lesions

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Wahl, Sharon, M.	Staff Fellow	LMI	NIDR
OTHER:	Oppenheim, Joost J.	Medical Officer - Research	LMI	NIDR
	Iverson, Gilbert M.	Staff Fellow	LMI	NIDR
	Kennedy, John B.	Biologist	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section : Cellular Immunology
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Investigations in progress in the Laboratory deal with the isolation of relatively pure populations of T and B lymphocytes which are then studied in vitro for their respective roles in the immune response. Mechanisms of activation of each of these cell types to proliferate and to produce a mediator chemotactic for homologous monocytes are being characterized. Agents capable of activating B cells to produce this mediator include: anti-immunoglobulins, aggregated immunoglobulins, antigen-antibody complexes, polymerized flagellin and endotoxins. Thus, agents interacting with surface receptors activate B cells. Finally, glucocorticosteroids have been studied and found to suppress production of chemotactic factors which may explain how these immunosuppressive agents interfere with cellular immune reactions.

NIDR CLASSIFICATION: 20312
TOTAL MAN YEARS : 1.50
PROFESSIONAL : 1.00
OTHER : .50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Sharon M. Wahl	3-28-71

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DA

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. DIR206a72

NIDR-72A- 047

TITLE OF PROJECT

Behavioral measurement of pain and temperature discrimination in monkey and human

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Beitel, Ralph E.	Staff Fellow	CD NA	NIDR
COPI:	Brown, Frederick J.	Electronic Engineer (Instru)	CD NA	NIDR
	Dubner, Ronald	Dent Dir, Ch Neur Mech Sect	CD NA	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Neurobiology and Anesthesiology Branch
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Monkeys are trained to detect and recognize warming or cooling stimuli applied to their face in order to receive a liquid reward. They are also trained to avoid potentially noxious or escape from noxious stimuli. Measurement of warm, cold, and escape thresholds are made. A corresponding study of pain and temperature thresholds in humans, utilizes the same stimulus parameters.

SPECIAL DESCRIPTORS:	NONE
NIDR CLASSIFICATION:	60430
TOTAL MAN YEARS:	2.0
PROFESSIONAL	1.0
OTHER	1.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Ralph E. Beitel

DATE: 3/28/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. OPD003C72

NIDR-72B- 048

TITLE OF PROJECT

Anatomical Studies of the Head of the Newborn Infant

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Bosma, James F.	Chief, Oral Pharyn	CD CIR	NIDR
COPI:	None			
OTHER:	Murayama, Diane R.	Illustrator	CD CIR	NIDR
COOP:	Pierce, Robert, Acting Chair. of Dept. of Radiology, Univ, ILL., Rockford, ILL.			
	Bartner, Howard, Div. of Res. Services, MAPB			
	Mainen, Michael, Private Practice, Minn.			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Invest. & Research Services
Section: Oral Pharyngeal Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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This is the fifth year of gross anatomical studies of the face, pharynx and cranium of the human fetus at term. Illustrations and written description of anatomical cross sections and matching X-ray tomograms are now in final stages of completion as an Atlas of Cranial Anatomical Section and Tomograms of the Human Newborn, authored by Robert Pierce (former Associate in Radiology at the Clinical Center), Michael Mainen (former Clinical Associate in this Section) and James Bosma.

Anatomical description and related illustrations of the newborn's upper pharyngeal area, including muscular palate and eustachian apparatus are now in progress. Six of a prospective 18 illustrations of this area are completed. A corresponding study of the lower pharynx and larynx will complete the material for a general anatomy book on the head of the newborn infant, excepting the brain.

SPECIAL DESCRIPTORS:	Children
NIDR CLASSIFICATION:	41220
TOTAL MAN YEARS:	2.25
PROFESSIONAL:	1:00
OTHER:	1.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	James F. Bosma	April 14

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBC301b72

NIDR-72B- 049

TITLE OF PROJECT

Comparative Aspects of the Mammalian Transglutaminases

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: S. I. Chung Senior Staff Fellow LB NIDR
OTHER: J. E. Folk Chief, Enzyme Chemistry S. LB NIDR

COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION Lab/Branch: Biochemistry
Section: Enzyme Chemistry
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

As an extension of a project carried out over the past few years, studies will be continued on the isolation and characterization of an important group of enzymes termed transglutaminases that catalyzed the formation of covalent cross-links between protein molecules. Three distinct classes of these enzymes in guinea pig and human tissues and organs have been defined in this laboratory. The isozymic nature of these enzymes is under investigation. The presence of high concentrations of a transglutaminase in red blood cells of human and guinea pig is under further study. Of particular interest are the roles of the individual transglutaminases in blood coagulation, wound healing, seminal plasma coagulation during fertilization, cell membrane formation, cross-linking of hair proteins, and covalent attachment of biological amines in proteins.

Biological control mechanisms, essential metal ion requirements, the immunochemical and the structural aspects of zymogen activation, active site and substrate specificities are under investigation. The biosynthesis and hormonal regulations of plasma pro-transglutaminase are under consideration to be investigated.

SPECIAL DESCRIPTORS: Blood
NIDR CLASSIFICATION: 20325
TOTAL MAN YEARS: 2.50
PROFESSIONAL: 1.50
OTHER: 1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Sook I. Chung	5/8/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LMI012 b72

NIDR-72B -050

TITLE OF PROJECT

Extracellular Polysaccharide Synthesis by Caries Producing Streptococci.

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Dr. Joseph E. Ciardi	Senior Staff Fellow	LMI	NIDR
COPI:	Dr. Charles L. Wittenberger	Research Microbiologist	LMI	NIDR
OTHER:	Dr. George Hagaage	Research Microbiologist	LBS	NIDR
	Mr. Alfred Beaman	Biological Laboratory Technician	LMI	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology & Immunology
Section: Microbial Physiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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The mechanisms by which extracellular polysaccharides are produced by various strains of S. mutans are being studied in order to better understand the processes of attachment of the organisms to the tooth surface and to each other. The extracellular glucosyltransferases have been extensively purified and their molecular structure, reaction kinetics, and physical properties are under investigation. Serological studies are being conducted with the purified glucosyltransferases to assess their immunological relatedness and to explore the feasibility of producing an effective vaccine against this group of organisms. Various inhibitors of glucan formation are also being sought as another approach to the effective prevention of microbial colonization of the tooth surface.

SPECIAL DESCRIPTORS: 0
NIDR CLASSIFICATION: 10250
TOTAL MAN YEARS : 2.50
PROFESSIONAL : 1.50
OTHER : 1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Joseph E Ciardi	3/25/7

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DA

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-OMS008c72

NIDR-72C-051

TITLE OF PROJECT

Immunochemical Studies of Sjögren's Syndrome

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Norman A. Cummings	Medical Officer	LOM	NIDR
COPI:	None			
OTHER:	T. M. Chused	Sr. Staff Fellow	LMI	NIDR
	T. M. Tarpley	Sr. Dental Surgeon	LOM	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The immunochemical aspects of salivary gland antigens will be assessed in Sjögren's syndrome. Ability to inhibit anti-salivary gland antibody in fluorescence or autoradiographic techniques will be used to identify the antigens isolated from the gland by column chromatography. Protein fractions from the gland will also be evaluated for their ability to stimulate transformation of lymphocytes from patients. An effort to isolate anti-salivary duct antibody by affinity chromatography will be made.

SPECIAL DESCRIPTORS:
NIDR CLASSIFICATION: 34300
TOTAL MAN YEARS: .75
PROFESSIONAL: .25
OTHER: .50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Norman A. Cummings, M.D.	3/29/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBS421b72

NIDR-72B-052

TITLE OF PROJECT

Cell Proliferation During Craniofacial Growth

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Hassell, John R.	Staff Fellow	LBS	NIDR
COPI:	King, C.T.G.	Research Physiologist	LBS	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Biological Structure
Section: Experimental Pharmacology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The importance of DNA synthesis to the growth of craniofacial structures in general and the primary and secondary palate in particular has not been determined. In addition drugs which appear to interfer with craniofacial growth are administered relatively early in gestation, when the small size of the developing head precudes direct dissection and quantitative analysis. For this reason, new methods for determining growth rates are being developed. One of these methods involve administering labeled thymidine on days 9-15 of gestation and measuring the specific activity of the DNA in the various embryo regions as well as the whole embryo on day 16. To define the length of isotope administration, the metabolic half life of thymidine is also being measured for each mode of administration. The relative growth of any region can then be determined by comparing the specific of the various regions to the whole embryo, in both control and experimental groups. The appearance of heterotopic cartilage as a result of vitamin A treatment is also being evaluated. This is being accomplished by following the synthesis of collagen, acid mucopolysaccharides and glycoproteins, both in vitro and in vivo, in vitamin A and control embryos.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 42220
TOTAL MAN YEARS: .65
PROFESSIONAL: .35
OTHER: .30

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	John R. Hassell	3/24/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DAT

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBC404b72

NIDR-72B -053

TITLE OF PROJECT

Studies of Ribosomal Proteins in Mammalian Cells

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Dr. S. Jakoby	Senior Staff Fellow	LB	NIDR
OTHER:	Dr. H. Cooper	Chief, Cell Biology S.	LB	NIDR

COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biochemistry
Section: Cell Biology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This study undertakes the isolation and characterization of proteins from the ribosomes and ribosomal subunits of HeLa cells and lymphocytes. Methods for the isolation of specific ribonucleoprotein particles are being developed. Evidence has been presented from this laboratory that certain unique particles participate in cell growth control, and may be the mechanism for shifting from the resting to the rapidly growing state in animal cells. Techniques which are being developed include:

1. Affinity chromatography of ribonucleoprotein fragments.

2. Separation of proteins from glycoproteins.

3. Resolution of glycoproteins with and without terminal sialic acid residues.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	41211
TOTAL MAN YEARS:	2.25
PROFESSIONAL:	1.25
OTHER:	1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Shelley B Jakoby	5/7/74

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-72B-054

Prev. Ser. No. DIR102b72

TITLE OF PROJECT

Time Lapse Photographic Studies of Aggregation and Differentiation in Dictyostelium Discoideum

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Love, Leslie L.	Biological Lab Tech -Biochem-	ODIR	NIDR
COPI:	Krichevsky, Micah I.	Chief, Environmental Mech. Sect.	ODIR	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Environmental Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

We have been able to grow five strains Dictyostelium discoideum in axenic liquid culture. Also, these strains can be grown on agar surfaces, but slowly. Thus, stock cultures of axenically grown strains can be maintained without the short term liquid cultures previously required.

The axenic strain (AX-1) responds chemotactically to cyclic AMP, almost like NC4 strain. However, the concentration required is both lower and critical. Too much cyclic AMP does not show chemotaxis even though the cells differentiate. We found that folic acid causes chemotactic responses at the same concentrations in both strains.

Folic acid, at the proper concentration, inhibited differentiation in the axenic strain without losing its chemotactic properties. The cells retained their motility and normal appearance although they do not differentiate at any time on agar.

Time lapse cinematography has shown that folic acid and cyclic AMP act at different stages of development. A cell suspension, placed on agar containing both chemotactic agents shows two concentric rings of cells. The outer ring has the same diameter change with time as that with folic acid alone. The inner ring corresponds to that obtained with cyclic AMP alone.

SPECIAL DESCRIPTORS:	NONE
NIDR CLASSIFICATION:	41211
TOTAL MAN YEARS:	1.00
PROFESSIONAL	.75
OTHER	.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR

Leslie L. Love

DATE

4-15-74

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LMI019b72

NIDR-72B-055

TITLE OF PROJECT

Transport and Metabolism of Hexitols in Streptococcus mutans

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Dr. James H. Maryanski	Staff Fellow	LMI	NIDR
COPI:	Dr. C. L. Wittenberger	Research Microbiologist	LMI	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION Laboratory: Microbiology & Immunology
Section: Microbial Physiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The transport of mannitol in Streptococcus mutans by a phosphoenolpyruvate-dependent phosphotransferase system has been demonstrated, and the properties of this enzyme system are being studied in relation to similar transport systems reported for other bacteria. Mutants of Streptococcus mutans unable to grow on mannitol are being studied to elucidate the enzymatic reactions involved in hexitol transport and metabolism. The effect of various metabolic intermediates on the regulation of the phosphotransferase system and on mannitol-1-phosphate dehydrogenase is currently under investigation.

SPECIAL DESCRIPTORS:	0
NIDR CLASSIFICATION:	10250
TOTAL MAN YEARS :	1.25
PROFESSIONAL :	1.25
OTHER :	0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	James H. Maryanski	3/26/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. DIR002a72

NIDR-72A-056

TITLE OF PROJECT

Laboratory Automation Software

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Medlin, Terry P.	Head, Scientific Unit	OD	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Office of the Director
Section: Data Processing Systems and Analysis
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

1. Multiprogramming Systems Software for the NIDR Laboratory Automation System: Maintenance of the OLERT multiprocessor real-time operating system. Modification of OLERT to allow interprocess communication via semaphores.

2. Neurophysiological Data Analysis Software: Maintain a series of programs to process and graph neurophysiological data. These programs run on the NIDR OLERT computer system. Extend to allow multiple graph overlays with flexible windowing.

3. Binary Synchronous Communications Software: Design and implementation of IBM compatible communications systems software for telephone communications between the NIDR OLERT computer system and the PDP-10 computer at the Division of Computer Research and Technology, NIH. Interface protocol will be that of an IBM 2780.

4. Development of a system implementation language for real-time environment.

SPECIAL DESCRIPTORS:	NONE
NIDR CLASSIFICATION:	10290
TOTAL MAN YEARS:	.50
PROFESSIONAL	.50
OTHER	0.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Terry P. Medlin	

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DAT

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBS421b72

NIDR-72B-057

TITLE OF PROJECT

Changes in the Macromolecular Constituents of Embryonic Connective Tissue in Experimentally Induced Cleft Palate of the Rat

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Pratt, Robert M.	Sr. Staff Fellow	LBS	NIDR
COPI:	Hassell, John R.	Staff Fellow	LBS	NIDR
OTHER:	King, C.T.G.	Research Physiologist	LBS	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Biological Structure
Section: Experimental Pharmacology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objective of this project is to examine the mechanism whereby diazo-oxo-norleucine (DON) inhibits the rotation and remodeling of the palatal shelves, thus causing cleft palate. DON inhibits both the synthesis of DNA and mucopolysaccharides in the palate and studies are being conducted to determine which effect is primarily responsible for cleft palate. Amino-imidazole-carboxamide (AIC), when coadministered with DON, prevents the cleft palate, and suggests that inhibition of DNA synthesis plays a major role in the etiology of the DON induced cleft palate.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 42220
TOTAL MAN YEARS: .75
PROFESSIONAL: .45
OTHER: .30

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Robert M. Pratt	3/28/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LMI022b72

NIDR-72B -058

TITLE OF PROJECT

Contribution of Nuts and Corn Mitogens to Gingival Inflammation

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Radenz, William	Guest Worker	LMI	NIDR
OTHER:	Oppenheim, Joost J.	Medical Officer - Research	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section : Cellular Immunology
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Periodontists have observed a significant incidence of "sterile" gingival abscesses that contain corn husks. The possibility of a causal relationship between the pathogenesis of this gingival inflammation and impacted food particles is being studied. Saline extracts of a variety of nuts and corn have therefore been tested and found to be mitogenic for lymphocytes, to stimulate the production of factors chemotactic for macrophages and to release histamine from basophiles of allergic subjects. The likelihood that some foods can directly cause tissue inflammation by nonspecific mitogenic activation of lymphocytes is being further studied.

NIDR CLASSIFICATION: 32200
TOTAL MAN YEARS : .75
PROFESSIONAL : .75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	William J. Radenz	28 MAR 7

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LMI023b72

NIDR-72B -059

TITLE OF PROJECT

Nature of Cytotoxic Lymphoid Cells and Mechanism of Antibody-Dependent Cell-Mediated Cytotoxicity

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Rosenstreich, David	Senior Staff Fellow	LMI	NIDR
OTHER:	Fridberg, Andrew P.	Biologist	LMI	NIDR
COOP :	Van Boxel, J.			
	NIAMD, NIH, Bethesda, Md.			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section : Cellular Immunology
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This laboratory has been studying the phenomenon of antibody-dependent cell-mediated cytotoxicity in the guinea pig. Two cell types are involved. One cell is a macrophage, and the other cell is a weakly adherent, nonphagocytic cell which has tentatively been labelled as a K-cell. Activated T-lymphocytes do not act as killer cells in this system.

NIDR CLASSIFICATION: 31200
TOTAL MAN YEARS : 1.50
PROFESSIONAL : .50
OTHER : 1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Doris Rosen	3/28/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

Prepared for the Science Information Exchange.

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LMI024b72

NIDR-72B -060

TITLE OF PROJECT

The Mechanism of Action of Lymphocyte Stimulation of Bacterial Endotoxins

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

:PI:	Rosenstreich, David	Senior Staff Fellow	LMI	NIDR
OTHER:	Mergenhagen, Stephan E.	Chief, Lab. of Micro. and Immunol.	LMI	NIDR
	Weedon, Lynda L.	Biologist	LMI	NIDR
COOP :	Nowotny, A.			
	Temple University School of Medicine, Phila, Pa.			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section : Cellular Immunology
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Previous work demonstrated that a purified bacterial glycolipid was mitogenic for lymphocytes. We have now found that a purely synthetic glycolipid, is also mitogenic. It is now possible to synthesize glycolipids with specific functional endotoxin-like properties but without other deleterious properties.

The ability of mouse lymphocytes to respond to endotoxin has been found not to depend on prior sensitization since cells from germ-free mice respond as well as those from conventionally reared animals.

The mouse lymphocytes response to endotoxin is under genetic control. Endotoxin responsiveness is controlled by an autosomal dominant gene in C3H/HEJ mice and by a sex-linked recessive gene in CBA/HN mice. The inability of mouse cells to respond to endotoxin in vitro has been found to correlate with certain in vivo activities of endotoxin such as LPS lethality.

NIDR CLASSIFICATION: 20314
TOTAL MAN YEARS : 1.50
PROFESSIONAL : .50
OTHER : 1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
		3/28/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LMI021b72

NIDR-72B-061

TITLE OF PROJECT

Complement Activation and its Relationship to the Inflammatory Response

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Sandberg, Ann L.	Research Biologist	LMI	NIDR
OTHER:	Bechtold, Judith A.	Chemist	LMI	NIDR
	Phillips, Jean, K.	Biologist	LMI	NIDR
	Mergenhagen, Stephan E.	Chief, Lab of Micro & Immuno	LMI	NIDR
	Raisz, Lawrence G.			(1)
COOP:	(1) University of Rochester, Rochester, N.Y.			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section : Humoral Immunity
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The mechanism by which complement activation at a cell surface results in prostaglandin synthesis and concomitant bone resorption in organ cultures is currently under investigation. Studies regarding the possible requirement for immunoglobulins in the activation of complement by endotoxin are being continued. The interaction of the different immunoglobulin classes with the complement system and the influence of antigenic structure on the mode of complement interaction are under examination.

SPECIAL DESCRIPTORS:	0
NIDR CLASSIFICATION:	20315
TOTAL MAN YEARS :	3.00
PROFESSIONAL :	2.00
OTHER :	1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Ann L Sandberg	3/26/74

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. DIR205b72

NIDR-72B-062

TITLE OF PROJECT

Correlation of Physiological and Anatomical Observations on Oral-Facial Skin Receptors

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Starkman, Sidney	Surgeon	CD NA	NIDR
COPI:	Sumino, Rhyuji	Visiting Associate	CD NA	NIDR
	Dubner, Ronald	Dent Dir, Ch Neur Mech Sect	CD NA	NIDR
	Gobel, Stephen	Sr Dental Surgeon	CD NA	NIDR
	Binck, Joan M.	Biologist	CD NA	NIDR
OTHER:	Munger, Bryce			(1)
COOP:	(1) Hershey Medical Center, Hershey, Pennsylvania			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Neurobiology and Anesthesiology Branch
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The oral-facial skin receptive fields of mechanosensitive trigeminal afferent nerve fibers, dissected from the infraorbital nerve in the monkey, are studied. At the termination of the experiment, these skin areas are surgically dissected for histological study with light and electron microscope techniques.

SPECIAL DESCRIPTORS: NONE
NIDR CLASSIFICATION: 60210
TOTAL MAN YEARS: .75
PROFESSIONAL .50
OTHER .25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Sidney Starkman (RD)

DATE: 3/28/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: CPR008b72

NIDR-72B-063

TITLE OF PROJECT

Occurrence of Oral Streptotocci in the oral cavity and feces of children aged 3 to 24 months

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Stiles, Horace McElreath	Senior Staff Fellow	CP PR	NIDR
OTHER:	None			
COOP:	C and Y Project No. 660, Robstown, Texas			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Etiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A study of sample parameters for a longitudinal investigation of the first appearance and subsequent prevalence of oral streptococci in children has been completed. The investigation now in progress involves monthly examination of oral swabs and feces collected from 30 children until the Streptococcus spp. sought is isolated from 3 successive monthly collected specimens.

Preliminary studies also involved the development of transport and culture techniques for the selective control of overgrowth by the Gram-negative flora in plate cultures.

SPECIAL DESCRIPTORS: Children
NIDR CLASSIFICATION: 10120
TOTAL MAN YEARS: 2
PROFESSIONAL: 1/4
OTHER: 1 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Horace McElreath Stiles	Apr. 18, 1974

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

NIH-1946 (FORMERLY PHS-166)
REV. 6-72

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-72A-064

Prev. Ser. No.: CPR009b72

TITLE OF PROJECT

Identification of S. mutans and other dental plaque Streptococci using cultural, biochemical and immunological methods.

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Thomson, L. Ariel	Senior Dental Surgeon	CP PR	NIDR
COPI:	Brunelle, Janet Ann	Statistician - Health	CP PR	NIDR
	Facklam, Richard	Microbiologist		(1)
	Cherry, William	Microbiologist		(2)
	Gherna, Robert	Microbiologist		(3)
COOP:	(1) (2) Center for Disease Control, Atlanta Georgia			
	(3) American Type Culture Collection, Bethesda, Maryland			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Research and Prevention
Section: Etiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The purpose of the present project is to provide identification criteria (with supporting data) for certain streptococci considered to be potentially cariogenic. In addition, the immunofluorescent capabilities of several laboratories have been joined in collaborative research designed to develop FA reagent grade conjugates specific for certain plaque streptotocci.

Numerical taxonomic methods, other computer techniques, as well as conventional methods are being used to analyze the data from over 700 strains to develop differentiating criteria. Colored plates are being prepared to portray representative colonial types.

Efforts in fluorescent antibody research have resulted in the development of improved immunization schedules, higher titered antisera, the optimal F/P ratio for conjugates and major advances in immunoabsorption methods to improve S. mutans conjugates. A new combined column serum fractionation method has been developed to obtain pure gamma globulin fractions.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10250
TOTAL MAN YEARS: 1 3/4
PROFESSIONAL: 3/4
OTHER: 1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	L Ariel Thomson	4-22-72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DAT

NIH-1946 (FORMERLY PHS-166)
REV. 6-72

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-OMS016c72

NIDR-72C-065

TITLE OF PROJECT

Clinical Evaluation of a New Type of Dental Radiographic System

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Webber, Richard L. Senior Dental Surgeon Chief of CIR CIR NIDR
COPI: None
Other: None
COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Investigations & Research Services
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A new type of radiographic system which couples an intraoral source of radiation to an extraoral transducer is to be tested clinically. The output of the device includes both conventional and Polaroid type radiographic displays. The latter are available seconds after exposure. The design provides for the production of images with far less radiation than required by conventional techniques.

Factors to be evaluated include task specificity, practical constraints, patient acceptance, training requirements, and diagnostic quality. Diagnostic performance is to be determined from radiographs of phantoms containing known pathology and the results are to be compared with comparable data produced conventionally.

NIDR CLASSIFICATION: 10400
TOTAL MAN YEARS: .25
PROFESSIONAL: .25
OTHER:

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Richard L. Webber	3/29/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-OMS017c72

NIDR-72C-066

TITLE OF PROJECT

Determination of Task-Specific Factors Influencing Diagnostic Performance from Radiographs

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Webber, Richard L. Senior Dental Surgeon Chief of CIR CIR NIDR
COPI: None
OTHER: None
COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION Lab/Branch: Clinical Investigations & Research Services
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Research is being directed toward the determination of factors limiting diagnostic performance from dental radiographs. Of specific interest, is the consideration of task-specific questions from the point of view of information theory.

Specific experiments involve selective manipulation of factors known to reduce the information capacity of radiographic displays and the determination of the effects (if any) on diagnostic performance by human interpreters. It is anticipated that such an approach will permit specification of diagnostically meaningful information in terms of spatial frequency spectra found to be essential for specific diagnostic tasks.

NIDR CLASSIFICATION: 10400
TOTAL MAN YEARS: .25
PROFESSIONAL: .25
OTHER

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Richard L Webber	3/29/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DA

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBS301b73

NIDR-73B-067

TITLE OF PROJECT

Studies on Polysaccharides Produced by oral Streptococci and Actinomycetes

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Bladen, Howard A.	Research Microbiologist	LBS	NIDR
COPI:	De Stoppelaar, J. D.	Visiting Associate	LBS	NIDR
OTHER:	None			
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Structural Interactions
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Numerous oral organisms are being surveyed for similarities or differences in the molecular composition of their soluble and cell bound polysaccharides by the use of concanavalin A. Concanavalin A binds specifically to branched chained polymers of glucose, fructose and mannose. Therefore, a reaction with concanavalin A reveals the presence of these saccharides. Caries-active streptococci will be surveyed for specific similarities which may reflect some important factor essential to the organisms caries activity. The concanavalin A binding by non-plaque forming mutants will be compared to the binding by parent strains. Lectins other than concanavalin A which bind specifically to different saccharides will be investigated as to their potential usefulness.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	10250
TOTAL MAN YEARS:	3.25
PROFESSIONAL:	1.50
OTHER:	1.75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
		3/4/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBS201b73

NIDR-73B-068

TITLE OF PROJECT

The Reactivity of Phosphorofluoridate with Calcium Phosphate Salts

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Eanes, Edward D. Chief, Molecular Structure Section, LBS NIDR
COPI: None
OTHER: None
COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The chemical interaction of phosphorofluoridate (PO_3F^{2-}) with amorphous calcium phosphate (ACP) and crystalline apatite (CA) is being studied. The extent of PO_3F^{2-} adsorption on ACP and CA, the stability of adsorbed PO_3F^{2-}, and the inhibition of adsorption by other anionic species are being investigated. PO_3F^{2-} reactivity will be correlated with the composition, texture and prior chemical history of ACP and CA.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10220
TOTAL MAN YEARS: .80
PROFESSIONAL: .40
OTHER: .40

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Edward D Eanes	3/27/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBS121b73

NIDR-73B-069

TITLE OF PROJECT

Biochemical and Ultrastructural Studies on Tissue Fixation by Protein Crosslinking Reagents

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Hand, Arthur R.	Senior Dental Surgeon	LBS	NIDR
COPI:	Hassell, John R.	Staff Fellow	LBS	NIDR
OTHER:	None			
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Experimental Morphology & Experimental Pharmacol
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Chemical fixation is an important aspect of the preparation of tissues for examination by light and electron microscopy. However, the mechanisms involved in the reaction of the fixative reagents with various tissue constituents to produce the image observed in the microscope are poorly understood. The objectives of this study are to determine the biochemical and ultrastructural effects of the reaction of various protein crosslinking reagents and other types of fixatives on tissue constituents and cellular structure. Current efforts are directed toward measuring the retention of enzymatic activity and the preservation of glycogen in tissues fixed with dimethyl suberimidate or glutaraldehyde. Future studies will be carried out utilizing different techniques to further characterize the reaction of these fixatives with whole tissue, cellular molecules, and purified proteins.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	34200
TOTAL MAN YEARS:	.60
PROFESSIONAL:	.35
OTHER:	.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Arthur R Hand	3/29/74

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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NOTICE OF RESEARCH PROJECT

Prepared for the Science Information Exchange.

Not for publication or publication reference.

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. CPR026c73

NIDR-73C-070

TITLE OF PROJECT

Evaluation of a combination of self-administered measures of fluoride exposure for control of dental caries in a non-fluoride area

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Horowitz, Herschel S.	Dent Dir, Chief,CPS	CP PR	NIDR
OTHER:	Heifetz, Stanley B.	Dental Director	CP PR	NIDR
	Meyers, Rhea	Public Health Analyst	CP PR	NIDR
	Driscoll, William S.	Sr Dental Surgeon	CP PR	NIDR
COOP:	Virginia Department of Health, Division of Dental Health and Albemarle-Charlottesville-Nelson Health District, and Nelson County Public School System			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Community Programs
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Base line dental examinations were conducted in October 1972, on approximately 2200 first- through twelfth-grade children in Nelson County, Virginia. All study participants in grades 1-6 chew daily in school under supervision of the classroom teacher an acidulated phosphate-fluoride (APF) tablet containing 1 mg. F, rinse for 30 seconds with the resulting solution and then swallow the material. Once a week in school the same children also swish 10 milliliters of a 0.2 percent sodium fluoride solution for 60 seconds and then empty the contents of the mouth into a cup. A fluoride-containing dentifrice is distributed to the same children for use at home, and they receive toothbrushes periodically to take home. County health authorities and the county public school system are responsible for developing an oral health education program designed for elementary grades. These combined preventive procedures will continue in the elementary schools for a minimum of ten years. Follow-up dental examinations will be carried out biennially in all schools. The first follow-up survey is planned for October 1974.

SPECIAL DESCRIPTORS: Human, Clinical Trial, Children
NIDR CLASSIFICATION: 10540
TOTAL MAN YEARS: 1
PROFESSIONAL: .5
OTHER: .5

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Herschel S. Horowitz	4/18/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

NIH - 1946 (FORMERLY PHS - 166)
REV. 6-72

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: CPR027c73

NIDR-73C-071

TITLE OF PROJECT

Evaluation of a combined program of school water fluoridation and sodium fluoride mouthrinsing for the control of dental caries

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Joly, Olga G.	Health Scientist Adm.	CP PR	NIDR
OTHER:	von Mohr, George			(1)
	Jackson, Douglas			(1)
COOP:	(1) North Carolina State Board of Health, Fayetteville, N. C.			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Community Programs
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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About 2500 children attending grades 1 through 12 at three schools in Robeson County, North Carolina, are exposed to 1) fluoridation of the school water supply at four and one-half times the level estimated to be optimum for community fluoridation in the same geographic areas, and 2) weekly mouthrinsing with 0.2% NaF solution. Teachers dispense 10 millimeters of solution to each participant-child and supervise the one-minute rinsing procedure which is carried out in the classroom. To evaluate the long-term benefits of the combined treatments on the prevalence of dental caries, pre-treatment clinical data will be compared with the data obtained every two years until the completion of the program in 1984. Base line examinations using the DMF tooth and surface index were conducted in September 1972. Arrangements are currently being made to conduct the September 1974 follow-up examinations.

SPECIAL DESCRIPTORS: Human, Clinical Trial, Children
NIDR CLASSIFICATION: 10540
TOTAL MAN YEARS: .25
PROFESSIONAL: .15
OTHER: .1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Olga G. Joly	April 18, 1974

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

NIH - 1946 (FORMERLY PHS - 166)
REV. 6-72

NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBS441b73

NIDR-73A-072

TITLE OF PROJECT

The Effect of Prolonged Gestation or Delayed Implantation on Reproductive Capacity and Oral Facial Development and Growth

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	King, Cecil T. G.	Research Physiologist	LBS	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Experimental Pharmacology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Phenothiazine derivatives induce the malformation of isolated cleft palate, without any other malformation, when administered at critical stages of organogenesis in the rat. These compounds stimulate their own metabolism so that chronic administration negates their teratogenic action. In addition, these compounds prolong gestation by prolonging the pre-implantation period.

SPECIAL DESCRIPTORS: Children
NIDR CLASSIFICATION: 41240
TOTAL MAN YEARS: .70
PROFESSIONAL: .50
OTHER: .20

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Cecil T. G. King	3/28/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DAT

PHS-166
REV. 5-70

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NATIONAL INSTITUTE OF DENTAL RESEARCH
U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBS204b73

NIDR-73B-073

TITLE OF PROJECT

X-ray Diffraction Studies of Bone Mineral in Human Disease

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Termine, John D.	Research Chemist	LBS	NIDR
COPI:	None			
OTHER:	Nylen, Marie U.	Chief, Bio Structure Lab	LBS	NIDR
	Avioli, L. V.			(1)
	Russell, J. R.			

COOP: (1 & 2) Jewish Memorial Hospital, Washington U. School of Medicine, St. Louis, Mo.

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Hydrazine extraction is used to prepare bone mineral specimens that are both free of protein and unaltered in physicochemical properties compared to native tissue. The deproteinated bone specimens are then examined by quantitative x-ray diffraction procedures measuring diffraction intensity and broadening. Conventional diffraction equipment is automated and computerized in order to time-average these data. The x-ray diffraction measurements accurately estimate both the quantity and average size (and/or perfection) of the apatite present in the biological specimen relative to synthetic standards of similar composition and crystal texture. Thus, the relative level of average mineral maturation is assessed for each deproteinated bone sample examined. These experimental procedures are being used to study bone degeneration and recovery in chronic uremia. Tetracycline effects on developing bone mineral maturation are also being examined.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	20324
TOTAL MAN YEARS:	1.00
PROFESSIONAL:	.30
OTHER:	.70

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	John D. Termine	3/28/74

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH
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Prepared for the Science Information Exchange.

Not for publication or publication reference.

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-LBS205b73

NIDR-73B-074

TITLE OF PROJECT

Physicochemical Studies of Protein-Mineral Interactions

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Termine, John D.	Research Chemist	LBS	NIDR
COPI:	None			
OTHER:	Eanes, E. D.	Chief, Molecular Structure Section	LBS	NIDR
	Peckauskas, R.			(1)
	Pullman, I.			(2)
COOP:	(1 & 2) Department of Radiology, New York Medical College, New York, N. Y.			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The structural interaction of mineral ions and mineral solids with synthetic and biological macromolecules is being studied by a number of physicochemical techniques including infrared spectroscopy, laser Raman spectroscopy, electron paramagnetic resonance spectroscopy and electron microscopy. The mineral ions encompass the alkaline earth metals and the HPO_4^{-2}, $H_2P_2O_7^{-2}$ and HCO_3^- anions, while the mineral solids include the synthetic amorphous and apatite calcium phosphates. The macromolecules include cationic, neutral and anionic proteins, both simple and complex, as well as model mono- and polyfunctional biopolymers. Macromolecular entropic, electrostatic and conformational influences on mineral ion/solid binding are under study. Mineral solid-protein fiber quaternary structure relationships are also being investigated as well as the alterations in this relationship induced by non-fibrous tissue protein components.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	20324
TOTAL MAN YEARS:	1.15
PROFESSIONAL:	.70
OTHER:	.45

NO1-DE-32418

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	John D. Termine	3/28/

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION D

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

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U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-OMS021c73

NIDR-73C-075

TITLE OF PROJECT

Baseline Studies of the Effect of Pilocarpine on Parotid Gland Function in Sjögren's Syndrome

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Wolf, Robert O.	Dental Director	LOM	NIDR
COPI:	None			
OTHER:	L. G. Anderson and J. Sydney Stillman			(1)
	Gerald S. Johnston			(2)
COOP:	(1) Department of Medicine, Robert B. Brigham Hospital, Boston, Mass.			
	(2) Nuclear Medicine Department, Clinical Center, NIH			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The therapeutic effect of pilocarpine on xerostomia of Sjögren's syndrome will be examined. Affected individuals will be compared to control individuals before and after a short course of pilocarpine therapy. Parotid gland function and saliva quality will be monitored by sialometry, scintigraphy and chemical analysis of the secretion.

SPECIAL DESCRIPTORS:	Human
NIDR CLASSIFICATION:	10400
TOTAL MAN YEARS:	.50
PROFESSIONAL	.25
OTHER:	.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Robert O. Wolf	3/29-74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-OMSO22c73

NIDR-73C-076

TITLE OF PROJECT

Amylase Isoenzymes in Cystic Fibrosis

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Robert O. Wolf	Dental Director	LOM	NIDR
COPI:	None			
OTHER:	Lynn M. Taussig, Richard Deckelbaum and Mimi M. Belmonte			(1)
COOP:	Montreal Children's Hospital, Montreal, Canada			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Separation of serum and urine amylase into pancreatic and salivary isoenzymes may be of diagnostic benefit. Pancreatic insufficiency, particularly patients with cystic fibrosis, are being assessed. The isoamylase patterns of duodenal fluid, serum, urine, along with their total amylase values are being evaluated. Other pancreatic enzymes and stool fat are also being evaluated.

SPECIAL DESCRIPTORS:	Human
NIDR CLASSIFICATION:	10400
TOTAL MAN YEARS:	.25
PROFESSIONAL:	.25
OTHER:	.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Robert O. Wolf	3/29-74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DAT

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: None

NIDR-74A-077

TITLE OF PROJECT

Factors influencing Transmission of S. mutans in the young rat

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Amsbaugh, Suzanne	Biologist	CP PR	NIDR
OTHER:	Larson, Rachel H.	Research Chemist	CP PR	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Preventive Methods Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The purpose of this study is to determine the earliest transmission of S. mutans to the young rat nursed by a mother infected with S. mutans and fed a supporting diet. Special attention will be given to the effect of such factors as age of animal, tooth development and variations in the diet.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10120
TOTAL MAN YEARS: 0.2
PROFESSIONAL: 0.1
OTHER: 0.1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Suzanne M Amsbaugh	4/25/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR- 74B-078

TITLE OF PROJECT

Light and electron microscopic observations of oral-facial skin receptors in the monkey

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Binck, Joan M.	Biologist	CD NA	NIDR
COPI:	Sumino, Rhyuji	Visiting Associate	CD NA	NIDR
	Gobel, Stephen	Sr Dental Surgeon	CD NA	NIDR
	Dubner, Ronald	Dent Dir, Ch Neur Mech Sect	CD NA	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Neurobiology and Anesthesiology Branch
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Oral-facial skin receptors, identified with physiological techniques, are studied histologically. Light and electron-microscopic techniques are utilized to study the morphological characteristics of nerve terminals activated by mechanical, thermal and noxious stimulation.

SPECIAL DESCRIPTORS:	NONE
NIDR CLASSIFICATION:	60210
TOTAL MAN YEARS:	.75
PROFESSIONAL	.25
OTHER	.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Joan M. Binck	3/28/7

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74A-079

TITLE OF PROJECT

Conference and Publication of Symposia

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Bosma, James F.	Chief, Oral Pharyn	CD CIR	NIDR
COPI:	Weiffenbach, James M.	Senior Staff Fellow	LMI	NIDR
OTHER:	None			
COOP:	Fogarty International Center National Institute of Child Health and Human Development			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Investigations & Research Services
Section: Oral Pharyngeal Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The Fourth Symposium on Oral Sensation and Perception: Development in the Fetus and Infant, November, 1972, is scheduled for press release by the Government Printing Office in June.

A Symposium on Development of Upper Respiratory Anatomy and Physiology, in Relation to Sudden Infant Death is scheduled April 4-6. This is under auspices of the NIDR, the National Institute of Child Health and Human Development, and the Fogarty International Center.

A Symposium on Development of Preference for Sweet Taste is scheduled for June. This is under joint sponsorship of the NIDR and the Fogarty International Center.

SPECIAL DESCRIPTORS: Children, Human
NIDR CLASSIFICATION: 41323
TOTAL MAN YEARS: 1.5
PROFESSIONAL: 1
OTHER: 0.5

PROFESSIONAL SCHOOL *(medical, dental, etc.)* **WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED**

SIGNATURE OF PRINCIPAL INVESTIGATOR James F. Bosma

DATE 4-20-72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74B-080

TITLE OF PROJECT

Virus-Induced Diseases of the Endocrine and Exocrine Glands

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Boucher, D. Wark	Senior Staff Fellow	LOM	NIDR
COPI:	Notkins, Abner Louis	Medical Director, Chief of LOM	LOM	NIDR
OTHER:	Brown, Tecolia I.	Bio Lab Tech	LOM	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The production of a diabetes-like syndrome in mice by a variant of encephalomyocarditis (EMC) virus seems to depend on genetic factors, including the sex and strain of the animal. One possibility for differences between various strains of mice which is being investigated is that subtle differences in the time of initiation and magnitude of the immune response may determine whether the virus can produce beta cell damage. Alternately, the possible effect of hormonal differences on the expression of the disease in male and female mice is being studied. Additional studies will be involved with determining whether the virus may persist in the pancreas of these animals at low levels or in a latent form.

SPECIAL DESCRIPTORS:
NIDR CLASSIFICATION: 30000
TOTAL MAN YEARS: 3.00
PROFESSIONAL 1.25
OTHER: 1.75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	D. Wark Boucher	4/2/74

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METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DA

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: None

NIDR-74A-081

TITLE OF PROJECT

Development of an Anti-caries Vaccine

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Bowen, William H.	Visiting Scientist	CP PR	NIDR
OTHER:	Boyd, Dale			(1)
COOP:	(1) Hazelton Laboratories			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A colony of 50 young monkeys of the species Macaca fascicularis is being established in Hazelton Laboratories. They are being imported directly from Malaysia to ensure that only animals which meet our specific requirements are included in the study. The monkeys will be vaccinated through various routes using a variety of antigens derived from Strep. mutans. In addition to determining the effect of the procedures on the incidence of dental caries, the effects on the microbial composition of plaque will also be studied. The immunoglobulin response will be monitored.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10570
TOTAL MAN YEARS: .5
PROFESSIONAL: .3
OTHER: .2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	William H. Bowen	April 18 1974

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: None

NIDR-74A-082

TITLE OF PROJECT

Prevalence of Root Caries and its Relationship to Other Oral Conditions

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Brunelle, Janet Ann	Statistician -Health-	CP PR	NIDR
COPI:	Carter, Col. H. Gray			(1)
	Lohse, Major Walter			(1)
COOP:	(1) Dept. of the Army, Dental Co., U.S.A. Fort Knox MEDDAC, Fort Knox, Kentucky			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Biometry
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

An epidemiologic survey to determine the prevalence of root caries among staff, trainees and retirees at Fort Knox was conducted. Data on coronal and root caries, recession, oral hygiene, gingivitis, periodontal disease, abutment and crowns was collected and is being analyzed. Distributions and relationships among the variables will be assessed.

SPECIAL DESCRIPTORS:	Human
NIDR CLASSIFICATION:	10100
TOTAL MAN YEARS:	.35
PROFESSIONAL:	.25
OTHER:	.1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Janet A. Brunelle	4/18/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION D/

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74B-083

TITLE OF PROJECT

Immune Responses to Herpes Simplex Infection

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Burns, William H.	Research Associate	LOM	NIDR
COPI:	Notkins, Abner Louis	Medical Director, Chief of LOM	LOM	NIDR
OTHER	Billups, Lloyd	Biologist	LOM	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Md., 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Mice are depleted of thymus-dependent immune responses by thymectomy, lethal irradiation with bone marrow reconstitution, and anti-lymphocyte sera. This results in increased susceptibility of the mice to herpes infection. Restoration of resistance by reconstitution of the mice with selected subpopulations of T-lymphocytes is being attempted to determine which lymphocytes are active in conferring resistance to this infection.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 31300
TOTAL MAN YEARS: 3.00
PROFESSIONAL: 1.25
OTHER: 1.75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	William H Burns	7/2/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-74B-084

Prev. Ser. No.

TITLE OF PROJECT

Autoimmunity in New Zealand Mice

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Chused, Thomas M.	Senior Staff Fellow	LMI	NIDR
COPI:	None			
OTHER:	Brown, Elinor	Biologist	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Microbiology and Immunology
Section: Clinical Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objective of this project is to determine the etiology of autoimmunity in New Zealand mice. The type of cell infiltrating the salivary glands and other tissues is being evaluated. A quantitative analysis of lymphocyte surface antigens and receptors is in progress. The difference from normal strains in their in vitro B cell responses is being evaluated.

SPECIAL DESCRIPTORS:
NIDR CLASSIFICATION: 34000
TOTAL MAN YEARS: 1.75
PROFESSIONAL: 0.75
OTHER: 1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Thomas M. Chused, M.D.	3/29/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DA

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74C-085

TITLE OF PROJECT

Studies on Sjogren's Syndrome

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Chused, Thomas M Senior Staff Fellow LMI NIDR
COPI: None
OTHER:
COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION Lab/Branch: Microbiology and Immunology
Section: Clinical Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The extra salivary complications lymphocyte abnormalities, dental sequellae, presence of viruses and therapy are being investigated.

SPECIAL DESCRIPTORS:
NIDR CLASSIFICATION: 34000
TOTAL MAN YEARS: 0.25
PROFESSIONAL 0.25
OTHER: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	T. Thomas M. Chused M.D.	3/29/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74C-086

TITLE OF PROJECT

Treatment of Aphthous Stomatitis

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Norman A. Cummings	Medical Officer	LOM	NIDR
COPI:	None			
OTHER:	E. A. Graykowski	Medical Director	LOM	NIDR
	Rickley Senning	Chief, Biometry Sec.	CPR	NIDR
COOP:	Larry Kleinman, Pharmacy, CC			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Therapeutic trials of steroids and tetracyclines will be carried out to assess effectiveness in treatment of aphthous stomatitis. This will be done in a double-blind manner, and results compared to placebo therapy.

SPECIAL DESCRIPTORS:	Clinical Trials, Human
NIDR CLASSIFICATION:	32400
TOTAL MAN YEARS:	.25
PROFESSIONAL:	.25
OTHER:	.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Norman A. Cummings, M.D.	3/29/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION D E

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev.Ser. No. None

NIDR -74B-087

TITLE OF PROJECT

Immunologic Injury to Platelets

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Drobis, Jerrery	Clinical Associate	LMI	NIDR
COPI:	Siraganian, Reuben P.	Medical Officer Research	LMI	NIDR
OTHER:	Levin, David P.	Biological Lab. Tech.	LMI	NIDR
COOP:	NONE			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Microbiology and Immunology
Section: Clinical Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Mechanisms of tissue injury and inflammation due to immune complexes is being studied in a model system utilizing rabbit or human platelets. Antigen-antibody complexes, endotoxin and leukocyte cell products cause platelet aggregation and release of pharmacologic mediators. The involvement of the complement and clotting systems in these reactions is being evaluated.

SPECIAL DESCRIPTORS: Human Blood
NIDR CLASSIFICATION: 20315
TOTAL MAN YEARS: 1.30
PROFESSIONAL: 0.80
OTHER: 0.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Jeffrey Drobis	3/29/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. - None

NIDR-74B-088

TITLE OF PROJECT

Chemical, Structural, and Morphological Studies on the Interaction of Apatitic Substrates with Calcium Phosphate Solutions.

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Eanes, Edward D.	Chief, Molecular Structure Section	LBS	NIDR
COPI:	None			
OTHER:	None			
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The interaction of aqueous solutions of calcium and phosphate ions with apatitic substrates is being studied. Parameters being investigated are the rate and extent of the interchange of ionic calcium and phosphate between solution and substrate, and the effects this interchange has on substrate morphology and structure. Particular attention is being directed to the mechanisms by which new material is accreted onto the apatitic substrate under conditions of solution supersaturation. The effect on apatite crystals of rapid, cyclical alterations in solution conditions such as can be affected by sudden pH changes is also being studied, as is the role of inorganic and bioorganic adducts in modifying the above parameters. The purpose of these studies is to establish the fundamental physicochemical mechanisms by which enamel apatite responds to changes in oral fluid environment.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	10220
TOTAL MAN YEARS:	.95
PROFESSIONAL:	.40
OTHER:	.55

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Edward D. Eanes	3/27/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DA

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74C-089

TITLE OF PROJECT

The Application of the NBT Test in Evaluating Transient Dental Bacteremia

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Fred, Stephen R.	SA Dental Surgeon	CD CIR	NIDR
COPI:	Chusid, Michael J.	Clinical Associate	LCI	NIAID
OTHER:	Sweet, James B.	Sr. Dental Surgeon	CD CIR	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Investigations & Research Services Branch
Section: Clinical Dental Services Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Serial NBT tests are performed on patients undergoing oral surgical procedures. The data will be evaluated to determine if the NBT test can detect acute bacteremia. Parallel cultural studies will be utilized comparatively to test the accuracy of the NBT test.

SPECIAL DESCRIPTORS: Human, Blood
NIDR CLASSIFICATION: 20313
TOTAL MAN YEARS: 1.0
PROFESSIONAL: 0.5
OTHER: 0.5

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Stephen R. Fred	3-29-74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74B-090

TITLE OF PROJECT

Cellular Immunity and Herpes Simplex Viral Infections

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Fujibayashi, Takashi	Visiting Fellow	LOM	NIDR
OTHER	Hooks, John J.	Senior Staff Fellow	LOM	NIDR
	Notkins, Abner Louis	Medical Director, Chief of LOM	LOM	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The relationship between the cellular and humoral immune response to Herpes Simplex Virus (HSV) is under study. In vitro proliferation of peripheral blood lymphocytes in response to HSV is being utilized to detect and quantitate immune recognition of viral antigens by sensitized T lymphocytes. The plaque neutralization test is being used to quantitate the humoral immune response. The effect of HSV antibody complexes (whole serum, IgG and IgM) on the cellular immune response is under investigation.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	31 2 00
TOTAL MAN YEARS:	1.00
PROFESSIONAL:	1.00
OTHER:	.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Takashi Fujibayashi	3-28-7

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74C-091

TITLE OF PROJECT

Investigations on the Etiology of Oral Mucosal Ulcerations

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Graykowski, Edward A.	Medical Director	LOM	NIDR
COPI:	None			
OTHER:	Norman A. Cummings	Medical Officer	LOM	NIDR
	John J. Hooks	Sr. Staff Fellow	LOM	NIDR
	Charles Daniels			
COOP:	Duke University, Durham North Carolina			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This project is concerned with the etiology of oral ulcerations produced by - 1) primary and recurrent herpes, 2) recurrent aphthous ulcers, and 3) Behcet's syndrome. The objectives of the project are: (1) to establish the salient clinical features of these diseases for differential diagnosis; (2) to establish the histopathologic aspects of the oral ulcerations; (3) to establish the role of predisposing factors in the etiology of these diseases; (4) to investigate the mechanism which governs recurrence; (5) to establish the use of laboratory procedures as an aid in diagnosis; (6) to identify and characterize the etiologic agent(s) and histopathologic mechanism in these diseases.

SPECIAL DESCRIPTORS: Human, Clinical Trials
NIDR CLASSIFICATION: 32200
TOTAL MAN YEARS: 2.00
PROFESSIONAL: 1.75
OTHER: .25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Edward A. Graykowski	3-29-74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74B- 092

TITLE OF PROJECT

Pathogenesis of Herpes Simplex and Other Viral Infections

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Hayashi, Kozaburo	Visiting Associate	LOM	NIDR
COPI:	Notkins, Abner Louis	Medical Director, Chief of LOM	LOM	NIDR
OTHER:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Our work has focused on understanding the pathogenesis of viral infections, using routine microscopy and immunofluorescence. Viruses under study include Herpes Simplex, Encephalomyocarditis, Mumps, and Coxsackie B group.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 31300
TOTAL MAN YEARS: 3.00
PROFESSIONAL: 1.25
OTHER: 1.75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Kozaburo Hayashi	5/3/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DA

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74A-093

TITLE OF PROJECT

Keratinization of Palate Epithelial Cells

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Hassell, John R.	Staff Fellow	LBS	NIDR
COPI:	Pratt, Robert	Sr. Staff Fellow	LBS	NIDR
	Cohen, Stanley			(1)
COOP:	(1) Vanderbilt University, Nashville, Tennessee			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Biological Structure
Section: Experimental Pharmacology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Previous work has shown that the Epidermal Growth Factor (EGF) inhibits epithelial cell death in shelves cultured in vitro. Electron microscopic examination of the midline epithelial cells revealed that the cells were actively undergoing the initial stages of keratinization. The epithelium and the mesenchyme are now being separated by proteolytic enzymes and further experiments are being conducted to determine the effect of EGF on the synthesis of proteins, glycoproteins, acid mucopolysaccharides and on the levels of cyclic AMP in these two regions of the palate. Radioactive precursors are being used to selectively label cellular components and the results are being evaluated by autoradiography, SDS gel electrophoresis and quantitative biochemistry.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 41211
TOTAL MAN YEARS: .70
PROFESSIONAL: .30
OTHER: .40

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	John R. Hassell	3/28/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74B-094

TITLE OF PROJECT

Aphthous Ulcers and Dermatologic Disorders

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Hooks, John J.	Senior Staff Fellow	LOM	NIDR
COPI:	Notkins, Abner Louis	Medical Director, Chief of LOM	LOM	NIDR
OTHER:	Geis, Shirley	Microbiologist	LOM	NIDR
	Graykowski, Edward A.	Dental Director, LOM	LOM	NIDR
	Hayashi, Kozaburo	Visiting Associate	LOM	NIDR
	Fujibayashi, Takashi	Visiting Fellow	LOM	NIDR
COOP:	Chused, Thomas M.	Senior Staff Fellow	LMI	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Recurrent aphthous ulcers, Behcet's disease and Sjogren's Syndrome are three disease states of unknown etiology with oral manifestations. Despite the frequency and severity of these disorders, very few attempts have been made to isolate viruses from patients with these diseases. The basic purpose of this study consists of the diagnosis and attempts to elicit chronic, slow or latent viruses from these patients. This approach will include attempts t demonstrate new antigens or antibodies in these patients.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 32400
TOTAL MAN YEARS: 3.00
PROFESSIONAL: 1.25
OTHER: 1.75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	John J Hooks	28 Mar 7

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION D/

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74B-095

TITLE OF PROJECT

Activation of Lymphocytes to Produce Antibodies and Mediators

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Iverson, Gilbert M.	Staff Fellow	LMI	NIDR
COPI:	Wahl, Sharon M.	Staff Fellow	LMI	NIDR
OTHER:	Oppenheim, Joost J.	Medical Officer - Research	LMI	NIDR
	Kerza-Kwiatecki, Margaret	Microbiologist	LMI	NIDR
	Kennedy, John B.	Biologist	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section : Cellular Immunology
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are to determine the cell surface requirements for activating lymphocytes. Experiments are underway to determine the degree of activation by such agents as anti-immunoglobulin, conconavalin A and phytohemagglutinin Experiments will be designed to correlate the degree of cross-linking of cell surface receptors with various parameters of activation such as antibody and mediator production and proliferation.

NIDR CLASSIFICATION: 20314
TOTAL MAN YEARS : 2.50
PROFESSIONAL : 1.25
OTHER : 1.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	GM Iverson	3-28-74.

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74C-096

TITLE OF PROJECT

Diagnosis and Treatment of Dento-Microbic Plaque Diseases

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Keyes, P.H.	Dental Director	CD CIR	NIDR
COPI:	None			
OTHER:	Robrish, Stanley A.	Research Microbiologist	CD CIR	NIDR
	Hageage, George J., Jr.	Research Microbiologist	LBS	NIDR
	Wright, William E.	Sr. Dent. Surg. Chief of CDS	CIR	NIDR
	Webber, Richard L.	Sr. Dent. Surg. Chief of CIR	CIR	NIDR
	Graykowski, Edward A.	Dental Director	LOM	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Investigations & Research Services
Section: Clinical Investigations
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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The objectives of this project are to improve the methods used to diagnose and to treat microbic plaque infections that destroy teeth and their supporting structures. Plaques from patients that have dental caries and destructive periodontitis are studied to determine the prevalence of Streptococcus mutans, various actinomyces, and motile forms. The prevalence of these populations and the appearance of lesions are followed as patients follow various experimental programs of dietary, mechanical and chemical therapy directed towards elimination and control of the potentially odontopathic microorganisms mentioned above. New and innovative cultural and microscopic methods are used to detect the presence of the microbes under consideration. Antibacterial agents and fluoride compounds are administered as adjuvants to conventional oral hygiene procedures and regulation of eating patterns.

NIDR CLASSIFICATION: 10400
TOTAL MAN YEARS: 1.00
PROFESSIONAL: 1.00
OTHER:

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Paul H. Keyes	29 Mar 19

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: None

NIDR-74A-097

TITLE OF PROJECT

Blocking in Dental Clinical Trials

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Korts, David C.	Staff Fellow	CP PR	NIDR
OTHER:	Senning, Rickley S.	Statistician -Health-	CP PR	NIDR
	Brunelle, Janet Ann	Statistician -Health-	CP PR	NIDR
	Reynolds, George R., Jr.	Statistician	CP PR	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Biometry
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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The purpose of this study is to determine whether the statistical technique of blocking should be used in the design of dental clinical trials and to provide specific recommendation for its implementation if it is judged desirable. Variables to be evaluated as potential blocking factors include: initial DMFS, surfaces at risk, age, sex, race, examiner, and various combinations of these variables. The use of covariables will also be considered, and the problem of lack of balance in blocks and/or groups will be studied.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 105A0
TOTAL MAN YEARS: .25
PROFESSIONAL: .15
OTHER: .1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	David C Korts	April 22, 1974

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

NIH-1946 (FORMERLY PHS-166)
REV. 6-72

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: None

NIDR-74A-098

TITLE OF PROJECT

Evaluation of Three Formulas for Estimating Mean DMFT from Percent of Individuals With One or More DMF Teeth

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	David C. Korts	Staff Fellow	CP PR	NIDR
COPI:	Sven Poulsen	Guest Worker	CP PR	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Biometry
Location: NIDR, NIH, Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK - *(200 words or less — Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

In 1944 Knutson described a formula for estimating age specific DMFT means from the percent of individuals in the age group having one or more decayed, missing or filled teeth. This formula, together with two other formulas are evaluated simultaneously for different age ranges, and for different allowable maximum percentages. Results indicate that appropriate restrictions of age range, and maximum percent of individuals with one or more DMF teeth, are far more important than choosing the "right" formula. The formula: $X = \frac{AY}{G-Y}$ with A = 3.117 and G = 179, where X is the estimated DMFT mean, and Y is the percent of individuals with one or more DMF teeth is, however, considered preferable to the other formulas based on ease of computation.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10140
TOTAL MAN YEARS: .25
PROFESSIONAL: .15
OTHER: .1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: David C Korts

DATE: April 22 M

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74A- 099

TITLE OF PROJECT

The Role of Trace Elements in Formation of the Primary Palate and Craniofacial Anomalies

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Kushner, David C.	Research Associate	LBS	NIDR
COPI:	King, C.T.G.	Research Physiologist	LBS	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Biological Structure
Section: Experimental Pharmacology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are: 1) development of an in vitro system for direct manipulation of rodent embryos across the critical period of primary palate development, and 2) investigation of the role of divalent cations (specifically endogenous zinc, magnesian and iron, and the environmental pollutants cadmium and lead) as trace elements in the formation of the normal and anomalous primary palate in species where clefts of the primary palate are not normally determined genetically.

SPECIAL DESCRIPTORS: Children
NIDR CLASSIFICATION: 42200
TOTAL MAN YEARS: .80
PROFESSIONAL: .50
OTHER: .30

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	David C. Kushner	3/28/74

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METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-74A-100

Prev. Ser. No. None

TITLE OF PROJECT

Investigation of Preimplantation Determinants of Teratogenesis and Embryolethality in Mammalian Embryos

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Kushner, David C.	Research Associate	LBS	NIDR
COPI:	King, C.T.G.	Research Physiologist	LBS	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Biological Structure
Section: Experimental Pharmacology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are: 1) to develop a system for direct manipulation of the preimplantation embryo including determination of A) in vivo factors in endocrine and drug-induced control of development and implantation; B) methods of in vitro development and micromanipulation of embryos; C) techniques of inter-strain, intra-species transplantation of embryos; and 2) determination of critical biochemical parameters involved in DNA replication and RNA transcription which are related to factors in embryolethality and sensitivity to teratogenesis.

SPECIAL DESCRIPTORS: Children
NIDR CLASSIFICATION: 41200
TOTAL MAN YEARS: .80
PROFESSIONAL: .50
OTHER: .30

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: David C. Kushner

DATE: 3/28/74

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DA

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: None

NIDR-74A-101

TITLE OF PROJECT

Gnotobiotic animal studies involving oral Streptococci

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Larson, Rachel H.	Research Chemist	CP PR	NIDR
OTHER:	Stiles, Horace McElreath	Senior Staff Fellow	CP PR	NIDR
	Hageage, George, Jr.	Research Microbiologist	CP GP	NIDR
	Tanzer, Jay			(1)
COOP:	Germfree Unit, Veterinary Resources Branch, NIH			
	(1) University of Connecticut, Health Resources Center School of Dental Medicine, Farmington, Conn. 06032			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Preventive Methods Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This work involves three phases:

a. Testing in gnotobiotic and barrier maintained rats the cariogenicity of several oral microorganisms.

b. Examining the relevance of symbiotic/antagonistic relationships of Streptococcus mutans and Streptococcus sanguis isolated from the same population to the cariogenicity of these organisms.

c. Evaluation of Actinomyces viscosus in the development of periodontal disease.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10250
TOTAL MAN YEARS: .45
PROFESSIONAL: .45
OTHER: None

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	[signature]	4/30/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: None

NIDR-74A-102

TITLE OF PROJECT

Generalized Computer Program for Statistical Evaluation of Longitudinal Clinical Trials

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Marthaler, Dr. Thomas	Guest Worker	CP PR	NIDR
OTHER:	Brunelle, Janet Ann	Statistician -Health-	CP PR	NIDR
	Reynolds, George R., Jr.	Statistician	CP PR	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Biometry
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A major redesign of an existing clinical trials computer program was undertaken. The objective was flexibility. Consequently, an investigator may designate particular dependent variables such as net increment DMFS, initial normal, erupting teeth, on a study as opposed to receiving total standard information which is not all needed or wanted. The PL/I program also allows the statistical output to be shown for many classifications of individuals such as age, sex, race, school, etc., at one time.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 105A0
TOTAL MAN YEARS: .25
PROFESSIONAL: .15
OTHER: .1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Th. Marthaler etc	4-18-74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DA

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-74A-103

Prev. Ser. No.: None

TITLE OF PROJECT

Synthesis of 8-Hydroxyquinolines with potential for long-term anticaries activity

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Mirth, Dale B.	Staff Fellow	CP PR	NIDR
OTHER:	Chite, Anthony F.	Bio Aid (Biochemistry)	CP PR	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Preventive Methods Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

In an effort to develop new antiplaque-anticaries agents, substituted 8-hydroxyquinolines are being prepared which have the potential for binding irreversibly to hydroxyapatite or proteins on the surface of a tooth. These compounds contain acid hydrolyzable bonds to allow for the slow release of the 8-hydroxyquinoline portion of the molecule at the time of acid challenge, which should result in the suppression of bacterial growth and subsequent plaque formation and caries development.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10510
TOTAL MAN YEARS: 1.0
PROFESSIONAL: .75
OTHER: .25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Dale B. Mirth	4/2 6/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: None

NIDR-74A-104

TITLE OF PROJECT

Evaluation of 8-Hydroxyquinolines for Controlling Experimental Dental Caries

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Mirth, Dale B.	Staff Fellow	CP PR	NIDR
OTHER:	Larson, Rachel H.	Research Chemist	CP PR	NIDR
	Chite, Anthony F.	Bio Aid (Biochemistry)	CP PR	NIDR
	Warner, Victor D.			(1)
COOP:	(1) Northeastern University, Boston, Massachusetts			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Preventive Methods Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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8-Hydroxyquinoline, an antibacterial agent with in vitro antiplaque activity, and promising analogs will be evaluated as anticaries agents in the rat model. An effort will be made to determine for each agent the optimal concentration, mode of application, and frequency of administration required to obtain the maximum amount of caries reduction.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	10510
TOTAL MAN YEARS:	0.5
PROFESSIONAL:	0.25
OTHER:	0.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Dale B. Mirth	4/24/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION D/

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NOTICE OF RESEARCH PROJECT

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Not for publication or publication reference.

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74B-105

TITLE OF PROJECT

Precocious Incisor Eruption in Newborn Rats

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Nylen, Marie U.	Chief, Lab of Bio Structure	LBS	NIDR
COPI:	Hassell, John R.	Staff Fellow	LBS	NIDR
OTHER:	King, C. T. G.	Research Physiologist	LBS	NIDR
	Cohen, S.			
COOP:	Vanderbilt University, Tenn.			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Experimental Morphology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Daily injections of the Epidermal Growth Factor (EGF) into newborn rats cause a precocious eruption of the lower incisors, opening of the eyes and keratinization of epithelial cells. Studies are currently underway to determine the basis for the precocious incisor eruption. Newborn rats were injected daily for 5 days with EGF (1µg/gm/day), and the animals were sacrificed on days 6 and 9. Projection x-ray microscopy, contract microradiography and optical microscopy are being utilized to determine the relationship of experimental and control incisors to various hard and soft tissues of the head and to assess differences in development of the head and teeth between experimental and control animals.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	41430
TOTAL MAN YEARS:	1.00
PROFESSIONAL:	.30
OTHER:	.70

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Marie U Nylen	3/29/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff ☐ Reactivated ☐ Special ☐ Research ☐ Other

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-74B-106

Prev. Ser. No. None

TITLE OF PROJECT

Cell Surface Glycoproteins in Palatal Development

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Pratt, Robert M.	Sr. Staff Fellow	LBS	NIDR
COPI:	Hassell, John R.	Staff Fellow	LBS	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Biological Structure
Section: Experimental Pharmacology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are: (1) to examine the chemical nature of the glycoproteins which are secreted to the cell surface of the medial edge of the secondary palate prior to fusion. This is being done by examining the incorporation of labeled precursors of glycoproteins by autoradiography, liquid scintillation counting, column chromatography and gel electrophoresis. Surface carbohydrates will also be examined by electron microscopy using stains such as concanavalin A and ruthenium red; (2) to examine the inhibition of palatal adhesion in vitro by diazo-oxo-norleucine (DON). The biochemical and morphological approach as in number 1 will be used to determine whether the inhibition in palatal adhesiveness by DON is due to an inhibition of glycoprotein secretion at the medial edge.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 41211
TOTAL MAN YEARS: .60
PROFESSIONAL: .40
OTHER: .20

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Robert M. Pratt	3/28/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DA

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74B-107

TITLE OF PROJECT

Regulation of Programmed Cell Death During Embryogenesis

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Pratt, Robert M.	Sr. Staff Fellow	LBS	NIDR
COPI:	Martin, George R.	Research Pharmacologist	LB	NIDR
OTHER:	Brown, Kenneth S.	Medical Director	HGB	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Biological Structure
Section: Experimental Pharmacology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are: (1) to examine whether cyclic adenosine 3'5' monophosphate (cAMP) plays a role in the programmed cell death in the epithelial cells of the medial edge of the palate prior to fusion. The levels of cAMP both in vivo and in vitro are being measured in the palatal shelves, and the effect that cAMP has on macromolecular synthesis ascertained. The palatal mesenchyme is being examined for a factor that regulates palatal epithelial cell proliferation by controlling the levels of intracellular cAMP and; (2) studies in vivo and in vitro using labeled thymidine are being conducted with the mouse mutant, hammer-toe in order to determine whether there is a defect in interdigital programmed cell death. The role that cAMP plays in this system will also be evaluated.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 41211
TOTAL MAN YEARS: .40
PROFESSIONAL: .30
OTHER: .10

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Robert M. Pratt	3/28/74

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74B-108

TITLE OF PROJECT

Immunogenicity of Long-Term Tissue Cultured Mouse Epithelial Explants

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Radenz, William	Guest Worker	LMI	NIDR
OTHER:	Iverson, G. Michael	Staff Fellow	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section : Cellular Immunology
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Epithelial cells of the attached gingiva of mice are being isolated and cultured. The effect of various exogenous and endogenous toxins on these culture cells will be evaluated for their possible role in periodontal disease.

Experiments are in progress to determine the antigenicity of epithelial explants in syngeneic and allogeneic mice. The graft rejection phenomenae will be evaluated for explants which have been maintained in tissue culture for varying time periods.

NIDR CLASSIFICATION: 20314
TOTAL MAN YEARS : 0.75
PROFESSIONAL : 0.75
OTHER : .00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	William H Radenz	28 MAR 7

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DAT

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74C-109

TITLE OF PROJECT

Screening of Dental Patients for the Presence of Streptococcus Mutans

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Robrish, Stanley A.	Research Microbiologist	CIR	NIDR
COPI:	None			
OTHER:	Keyes, P.H.	Dental Director	CIR	NIDR
	Webber, Richard L.	Sr. Dent. Surg. Chief of CIR	CIR	NIDR
	Hageage, George J., Jr.	Research Microbiologist	LBS	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Investigations & Research Services
Section: Clinical Investigations
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The project involves an estimation of the numbers and Bratthall serologic types of Streptococcus mutans obtained from a variety of the patients seen in the dental clinic. The presence of S mutans and S mutans serotypes are to be related to the clinical manifestations of caries in these patients. From this information we hope to gain further insight about the specificity of this suspected odontopath. Other data available from patient records, such as demographic information, manifestations of other diseases, and the presence or absence of specific medication or therapy will be used to develop a better understanding of the ecology of the organism. The systematics of the natural isolates identified as S mutans will be studied intensively in an attempt to determine the significance of the Bratthall classification and its clinical implications.

SPECIAL DESCRIPTORS: Clinical Trials, Human
NIDR CLASSIFICATION: 10250
TOTAL MAN YEARS: 1.00
PROFESSIONAL: .75
OTHER: .25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Stanley A. Robrish	3-29-74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74B-110

TITLE OF PROJECT

Detection of Viral Antigens and Antiviral Antibody in Herpes Simplex Viral Infections

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Rosenthal, Joel D.	Biologist	LOM	NIDR
COPI:	Notkins, Abner Louis	Medical Director, Chief of LOM	LOM	NIDR
OTHER:	Hayashi, Kozaburo	Visiting Associate	LOM	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Viral antigens and antiviral antibody can be rapidly detected and quantitated using rapid and simple micro-radioimmunoassays. The binding of radiolabeled antiviral antibody or anti-gamma globulin to fixed viral antigens are used in the direct, indirect, and inhibitio tests.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 31400
TOTAL MAN YEARS: 1.00
PROFESSIONAL: 1.00
OTHER: .00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Joel Rosenthal	3/29/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74B-111

TITLE OF PROJECT

Diseases of the Salivary Gland and Pancreas

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Ross, Michael E.	Research Associate	LOM	NIDR
COPI:	Notkins, Abner Louis	Medical Director- Chief of LOM	LOM	NIDR
OTHER:	Wolf, Robert O.	Dental Director	LOM	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of our work cover several facets of the endocrine and exocrine glands: 1) to establish an animal model for mumps infection and to explore its ramification; 2) to investigate some of the factors involved in the development of diabetes mellitus in mice following EMC virus infection; 3) to study the isoamylases in disease states and in normals, so that these isoenzymes can be used as markers for salivary and pancreatic diseases.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	34400
TOTAL MAN YEARS:	3.00
PROFESSIONAL:	1.25
OTHER:	1.75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	M E Ross	5/3/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

:ev. Ser. No.: None

NIDR- 74C-112

:LE OF PROJECT

:reening of Anticaries Agents

/E NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER :OFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

.I.	Shern, Roald J.	Dental Director	CP PR	NIDR
THER:	Greenman, Vivian	Microbiologist	CP PR	NIDR
	Miller, Carol	Biologist	CP PR	NIDR

AME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Preventive Methods Development
Location: NIDR, NIH, Bethesda, Maryland 20014

IMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in e bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

'he objective of this project is to identify agents suitable for short term clinical rials. The materials screened belong to two general categories, cationic antiseptics nd antibiotics. Screening is conducted both in vitro and in animals. The in vitro hase screens on such parameters as adsorption, minimal inhibitory concentration and iodification of enamel dissolution rate. The animal phase measures caries control nd plaque control and also monitors untoward effects such as acute toxicity and taining.

SPECIAL DESCRIPTORS: Human, Clinical Trials
NIDR CLASSIFICATION: 10510
TOTAL MAN YEARS: 0.9
PROFESSIONAL: 0.3
OTHER: 0.6

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Roald J Shern	April 19, 72

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UPPORTING AGENCY

ETHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

UNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: None

NIDR-74C-113

TITLE OF PROJECT

Short-term clinical trials of antiplaque agents

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Shern, Roald J.	Dental Director	CP PR	NIDR
OTHER:	Miller, Carol	Biologist	CP PR	NIDR
	Joly, Olga G.	Health Scientist Adm.	CP PR	NIDR
	von Mohr, George			(1)
	Defever, C. J.			(2)

COOP: (1) North Carolina State Board of Health
(2) University of Detroit School of Dentistry

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Preventive Methods Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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The objectives of this project are: (1) to identify, adapt and pretest in the laboratory, measurements of response variables other than plaque bacteria speciation, cytologic changes and pH modification; (2) to conduct short term clinical studies of agents which might be capable of restricting plaque and caries. These studies would measure various safety and efficacy parameters of antiplaque agents.

SPECIAL DESCRIPTORS: Human, Clinical Trials
NIDR CLASSIFICATION: 10520
TOTAL MAN YEARS: 0.5
PROFESSIONAL: 0.3
OTHER: 0.2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Roald J Shern	April 19, 1974

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74B-114

TITLE OF PROJECT

Control Mechanisms of IgE Production

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Siraganian, Reuben P.	Medical Officer Research	LMI	NIDR
COPI:	Drobis, Jeffery	Clinical Associate	LMI	NIDR
OTHER:	Fischler, Cynthia	Medical Technician Micro	LMI	NIDR
	Levin, David P.	Biological Lab. Tech.	LMI	NIDR
COOP:	NONE			

NAME AND ADDRESS OF APPLICANT INSTITUTION Lab/Branch: Microbiology and Immunology
Section: Clinical Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The mechanisms that control IgE antibody production are under study utilizing a model system in mice. Current emphasis is on the measurement of specific IgE produced on challenge by antigen. An assay for quantitating total IgE production is under development. Studies are under way to determine the genetic control mechanisms that determine the amout of IgE produced. In vitro studies in tissue culture are attempting to determine the role of T and B cells in the control of this antibody production and the mechanisms involved in its turn off.

SPECIAL DESCRIPTORS:
NIDR CLASSIFICATION: 20314
TOTAL MAN YEARS: 1.90
PROFESSIONAL: 0.90
OTHER: 1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
		3/29/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-74A-115

Prev. Ser. No.: None

TITLE OF PROJECT

The effect of Actinobolin alone and in combination with fluoride on caries experience in rats

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Stiles, Horace McElreath	Senior Staff Fellow	CP PR	NIDR
OTHER:	None			
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research, NCP
Section: Etiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Actinobolin is an experimental drug (IND applied for) developed originally as a potential anti-tumor agent. It appears to have an inhibitory effect of Streptococcus mutans and has been claimed to prevent the development of caries in rats. This study is attempting to reproduce the results of unconfirmed studies and to investigate additive effect of fluoride at varying levels.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	10510
TOTAL MAN YEARS:	.25
PROFESSIONAL:	.13
OTHER:	.12

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Horace McElreath Stiles	Apr. 13, 1974

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 6-72

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: None

NIDR-74A-116

TITLE OF PROJECT

The Effect of Cyancobalamin in Caries Development in the Rat

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Stiles, Horace McElreath	Senior Staff Fellow	CP PR	NIDR
OTHER:	None			
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research, NCP
Section: Etiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This study examines the effect of cyancobalamin on the implantation and aggregation of "caries-inducing" streptococci in the rat and its effect on caries development.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10510
TOTAL MAN YEARS: .25
PROFESSIONAL: .13
OTHER: .12

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Horace McElreath Stiles	Apr. 18, 1972

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: None

NIDR-74A-117

TITLE OF PROJECT

The effect of fluoride on the recovery of Ca^{45} from rats' teeth incubated with Streptococcus mutans

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Stiles, Horace McElreath	Senior Staff Fellow	CP PR	NIDR
OTHER:	Barry, Sue-ning			(1)
COOP:	(1) University of Maryland Dental School			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Etiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Teeth formed in the presence and absence of fluoride are being examined for the release of Ca^{45} when incubated with a cariogenic streptococcus in a medium containing known concentrations of fluoride.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	10220
TOTAL MAN YEARS:	.13
PROFESSIONAL:	.12
OTHER:	0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Horace McElreath Stiles	Sept. 15, 1974

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74C-118

TITLE OF PROJECT

Relationship of the Use of Antiseptics Prior to Oral Surgery and Bacteremia

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Sweet, James B.	Sr. Dental Surgeon	CD CIR	NIDR
OTHER:	Brenner, V. J.	Assistant Chief, CP	CP	CC
	Keyes, Paul H.	Dental Director	CD CIR	NIDR
	Robrish, Stanley A.	Research Microbiologist	CD CIR	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Investigations & Research Services Branch
Section: Clinical Dental Services Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Bacteremias are studied after various presurgical procedures are performed with various antiseptic solutions and again after oral surgery operations are performed within the oral cavity. The data will be evaluated for the variation in the distribution of bacteremias both as a factor of time and which presurgical procedure was performed. The predominant organisms will also be examined.

SPECIAL DESCRIPTORS: Human, Blood
NIDR CLASSIFICATION: 20313
TOTAL MAN YEARS: 1.00
PROFESSIONAL: 0.75
OTHER: 0.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
		3/29/71

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74C-119

TITLE OF PROJECT

Effect of Lavage Volumes in Third Molar Surgery

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Sweet, James B.	Sr. Dental Surgeon	CD CIR	NIDR
OTHER:	Beck, William D.	Dental Surgeon	CD CIR	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Investigations & Research Services Branch
Section: Clinical Dental Services Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Individuals from ages 15-30 years with bilateral, third molar impactions, indicated for extraction are examined postoperatively for infection and/or localized osteitis. Impacted teeth are removed and the alveolus is immediately irrigated with either high or low volumes of normal saline solution. Five day postoperative healing results are also being examined.

SPECIAL DESCRIPTORS: Human, Blood
NIDR CLASSIFICATION: 20320
TOTAL MAN YEARS: 1.0
PROFESSIONAL: 0.5
OTHER: 0.5

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
		3/29/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-74C-120

Prev. Ser. No. None

TITLE OF PROJECT

Sjögren's Syndrome in Humans and Animals

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Tarpley, Thomas M. Jr.	Sr. Dental Surgeon	LOM	NIDR
COPI:	Hayashi, Kazaburo	Visiting Scientist	LOM	NIDR
OTHER:	Ellis, Royd	Histopathology Technician	LOM	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are: (1) To establish an animal model for the detection of antisalivary duct antibody and determine the possible cross-reactivity with human sera; (2) to study the pathogenesis of Sjögren-like syndrome developing in the New Zealand mouse; (3) to study the possible etiological agents in NZB mice and humans.

SPECIAL DESCRIPTORS:	Human
NIDR CLASSIFICATION:	34300
TOTAL MAN YEARS:	1.00
PROFESSIONAL:	.50
OTHER:	.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Thomas M Tarpley Jr	

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DA

PHS-166
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NATIONAL INSTITUTE OF DENTAL RESEARCH

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Serial No. None

NIDR-74C-121

TITLE OF PROJECT

Intra-oral Skin Grafts in Post Surgical Cancer Patients

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Tarpley, Thomas M. Jr.	Sr. Dental Surgeon	LOM	NIDR
COPI:	Dellon, Arnold L.	Sr. Surgeon	SURG	NCI
OTHER:	Ellis, Royd	Histopathology Tech.	LOM	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are to evaluate the use of histological techniques to detect changes of full and split thickness grafts in the oral environment following major cancer surgery.

SPECIAL DESCRIPTORS:	Human
NIDR CLASSIFICATION:	33400
TOTAL MAN YEARS:	.75
PROFESSIONAL:	.50
OTHER:	.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Thomas M. Tarpley Jr.	

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74B-123

TITLE OF PROJECT

Latent Infection of Sensory Ganglia with Herpes Simplex Virus

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Walz, M. Antoinette	Staff Fellow	LOM	NIDR
	Price, Richard	Guest Worker	LOM	NIDR
COPI:	Notkins, Abner Louis	Medical Director, Chief of LOM	LOM	NIDR
OTHER:	Wohlenberg, Charles R.	Biologist	LOM	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are the following: 1) to establish a laboratory model of latent herpes simplex infection of sensory ganglia following inoculation by different routes; 2) to study the latency in sacral sensory ganglia following vagino-cervical infection with herpes simplex virus types 1 and 2; and 3) to determine, using this laboratory model, the factors involved in viral reactivation.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	31300
TOTAL MAN YEARS:	4.00
PROFESSIONAL:	2.25
OTHER:	1.75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	M. Antoinette Walz Richard W. Price	3/28/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: none

NIDR-74A-122

TITLE OF PROJECT

Development of Bacteriologic Methods for field studies investigating the etiology of dental caries

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Thomson, L. Ariel	Senior Dental Surgeon	CP PR	NIDR
COPI:	Little, Wayne	Microbiologist	CP PR	NIDR
	Benedict, Frances	Microbiologist	CP PR	NIDR
OTHER:	Socransky, S. S.	Dental Investigator		(1)
COOP:	(1) Forsyth Dental Center, Boston, Massachusetts			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Research and Prevention
Section: Etiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are: (1) to develop improved or optimal plaque dispersion methods using sonication techniques, different gaseous environments, or the addition of chemical-enzymatic additives to the dispersion solution; (2) to assess the role of colony crowding on agar plates upon colony morphology and the selective inhibition of certain streptococci; (3) to evaluate three selective broths as rapid presumptive tests for the presence of S. mutans in plaque samples.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10250
TOTAL MAN YEARS: .40
PROFESSIONAL: .25
OTHER: .15

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	L. Ariel Thomson	4-22-74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-74B-124

Prev. Ser. No. None

TITLE OF PROJECT

Oral Reflexes of the Infant

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Weiffenbach, James M.	Senior Staff Fellow	LMI	NIDR
COPI:	None			
OTHER:	Thach, Bradley T.	Senior Staff Fellow	LMI	NIDR
COOP:	Dept. of Pediatrics, National Naval Medical Center			
	Dept. of Pediatrics, D.C. General Hospital			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Investigations & Research Services
Section: Oral Pharyngeal Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The discrete lateral tongue movement of the human newborn initially described as a part of this project continues as the primary indicator response in a developing psychophysics of the neonate's oral sensitivity. The dependence of response on the intensity of a touch stimulus demonstrated in term infants has been replicated in low birthweight infants as has the decrement in response with repeated elicitation. Serial observation at 2 week intervals indicate intra-individual stability of measures of lingual tactual sensitivity based on this reflex.

The elicitation of tongue movements by individual drops of fluid placed on the tonque is initially independent of taste. However, response occurrence is a function of the glucose solution concentration of test drops administered after sensitivity to drops of water has been reduced by repeated stimulation. Male infants show a stronger effect of stimulus concentration on post criterion response, however, they also require fewer stimulus to reach our criterion. Thus, the observed sex differences may reflect difference in habituation rather than taste. Studies using non-sweet tastant are underway.

Recording made with the aid of infra-red television provides demonstration materials and an opportunity to examine other aspects of facial response.

SPECIAL DESCRIPTORS: Children
NIDR CLASSIFICATION: 41323
TOTAL MAN YEARS: 1.25
PROFESSIONAL: 1.00
OTHER: 0.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	James M. Weiffenbach	29 March 7

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-74A-125

TITLE OF PROJECT

Cyclophosphamide Induced Cranial Facial Malformations in Animals

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Wilk, Ann L.	Research Chemist	LBS	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Biological Structure
Section: Experimental Pharmacology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Administration of cyclophosphamide, at critical times of gestation, can produce either generalized or discrete cranial facial malformations in rats and rabbits. Present investigations are concerned with distribution, metabolism and possible activation of cyclophosphamide in various maternal and embryonic tissues. Future work will focus on the susceptibility or resistance of differentating cells to cyclophosphamide treatment.

SPECIAL DESCRIPTORS: Children
NIDR CLASSIFICATION: 42230
TOTAL MAN YEARS: .70
PROFESSIONAL: .50
OTHER: .20

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Ann Louise Wilk	3/25/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.

NIDR-74B-126

TITLE OF PROJECT

Mechanisms of Macrophage Activation by Mitogens and Antigens

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Wilton, Mark	Research Immunologist	LMI	NIDR
OTHER:	Rosenstreich, David	Senior Staff Fellow	LMI	NIDR
	Oppenheim, Joost J.	Medical Officer - Research	LMI	NIDR
	Schecter, Robert L.	Biologist	LMI	NIDR
COOP :	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section : Cellular Immunology
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

One pathway for activation of macrophages by endotoxin or specific antigens was shown to depend on prior activation of B and T lymphocytes respectively, which then produced a soluble factor which activate macrophages. This was measured by ^{14}C glucosamine incorporation by the macrophage. Alternatively, a direct effect of endotoxin and antigen on macrophages was also shown by measuring muramidase (lysozyme) release which can occur as early as one hour after the addition of endotoxin. The relationships and heterogeneous manifestations of indirect and direct mechanisms of macrophage activation are being explored.

NIDR CLASSIFICATION:	20314
TOTAL MAN YEARS :	2.00
PROFESSIONAL :	1.50
OTHER :	0.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Mark Wilton	3/29/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

PART II

NATIONAL INSTITUTE OF DENTAL RESEARCH

ANNUAL REPORT

NATIONAL CARIES PROGRAM

July 1, 1973 - June 30, 1974

Compiled by

Dental Research Data Officer

National Institute of Dental Research

National Institutes of Health

Bethesda, Maryland

PREFACE

The NIDR Annual Report is intended to capture in printed form the essence of the Institute's total activities during the course of one fiscal year. The present format has evolved from our desire to make the Report more palatable to the reader, a better reference tool for its users, and less burdensome in preparation for its contributors.

A major change in compilation has been made in this issue to accommodate our several uses of the completed document. The Report for FY 1974 has been prepared in organizationally distinctive Parts to facilitate selective distribution to those who are concerned with or require as a working instrument less than the total publication. These are: Part I, Office of the Director, Research Projects and Indexes; Part II, National Caries Program; Part III, Extramural Programs; Part IV, Intramural Research; and Part V, Contracts.

For the third year, we have continued the practice of using a modified SSIE Notice of Research Project form (PHS 166) for the Individual Project Report. These are collected together as a section of Part I. This section, on blue paper, is accompanied by a number of indexes, for ease of retrieval and analysis, and a Classification Guide to Subjects and Categories.

We apologize in advance for any errors that may have escaped our attention and would appreciate your comments and suggestions so that we may continue to improve this document in the future.

Seymour J. Kreshover, D.D.S., M.D.
Director
NIDR

CONTENTS

PART I - OFFICE OF THE DIRECTOR

PART I - RESEARCH PROJECTS AND INDEXES

PART II - NATIONAL CARIES PROGRAM PAGE

Preface iii

Contents v

Report of the Associate Director 1

Scientific Activities 4

Strategy I: Combat the Microbial Agent 6

Strategy II: Increase Tooth Resistance 15

Strategy III: Modify the Diet 19

Strategy IV: Develop Improved Delivery Systems for Caries Prevention 21

PART III - EXTRAMURAL RESEARCH

PART IV - INTRAMURAL RESEARCH

PART V - COLLABORATIVE RESEARCH PROJECTS

Report of Associate Director

National Caries Program

The National Caries Program is a highly-targeted effort whose mission is the elimination of dental caries as a public health problem in the United States. The general strategy of the Program is to accomplish this mission by developing agents and technics to prevent the incidence of caries, and to promote their widespread acceptance and use by the public.

A broad and detailed Program Strategy has been developed with extensive advice from the dental scientific community and is implemented through the conduct of direct operations research, research grants and research and development contracts. All three mechanisms are closely integrated and used in complementary fashion to achieve specific program goals.

Program progress and plans are reviewed by frequent workshops and symposia at which expert scientific consultants examine and advise on specific program segments, and by the Dental Caries Program Advisory Committee and the National Advisory Dental Research Council at the regularly scheduled meetings of these standing advisory bodies.

During the past year the National Caries Program made significant advances toward organizational functional stability. Dr. William F. Bowen, an internationally recognized caries researcher, was appointed Acting Chief, Caries Prevention and Research Branch, a crucially important position which had been vacant for nearly a year. As the year ended, a long search for adequate laboratory facilities for that Branch was successfully ended with acquisition of space in the Auburn Building. The release of impounded funds late in the year made it possible, for the first time, to award a substantial number of new research grants in high priority Program areas.

The year, however, was not without problems. As a result of stringent personell ceilings, key vacancies continued to exist in the Biometry Section and on the Contract Project Scientist staff, and the position of Chief, Etiology Section remained unfilled. Nevertheless, Program staffing and operations approached, for the first time, that which had been intended at its initiation two years earlier.

Research continued with several promising new fluoride compounds, notably the amine fluorides, ammonium fluoride and titanium tetrafluoride. Results of NCP studies, as well as several conducted in Europe produced convincing evidence that weekly or fortnightly mouthrinsing with dilute solutions of sodium fluoride may be a highly effective caries prevention measure, particularly from a cost/benefit standpoint, when used in a school setting. Plans to promote widespread use of this technic through community demonstration programs were therefore begun.

Results of research from several sources strongly suggested the somewhat disappointing conclusion that replacement of sucrose in snack foods by other simple sugars would have little effect in reducing caries incidence. Plans in this direction were therefore re-evaluated, and research efforts have been intensified on the commercial feasibility and disease-reducing potential of non-carbohydrate sweeteners, including the protein, Monellin.

Considerable progress was made in establishing a dialogue with pharmaceutical firms having interest in the development of antibacterial compounds for possible oral use. Plans for a collaborative preclinical and clinical screening program for such drugs were drafted with extensive input from both industrial and university scientists. The NCP screening program is thus expected to be sharply expanded during FY 1975, and the search for safe, effective methods of antiplaque chemotherapy to be greatly enhanced. At least twelve such compounds have already emerged from preclinical screening and are awaiting Investigative New Drug Clearance for short-term human trials.

Efforts to determine the feasibility of a vaccine to prevent caries were considerably expanded as a result of continuing encouraging results from experiments with both rodents and primates. Through new contracts, grants and Direct Operations projects, such questions as the antigenic properties of different fractions of oral bacterial cells and enzymes, the feasibility of intraductal (parotid) immunization, immunoglobulin levels in dental plaque and the effect of secretory antibody on bacterial adherence to the tooth are all under intensive study.

Community demonstration projects involving combinations of available preventive technics received increased support, especially several which are primarily concerned with the cost and personnel needs for such programs compared to their effectiveness. The problems attending the delivery, acceptance and public use of caries preventive technics are assuming increasing importance to the NCP, as Program research activities begin to yield agents of proven clinical efficacy.

During the year workshops and symposia were convened in several areas:

Dietary Modification and Caries	2 workshops
Physicochemical Mechanisms of Caries	Symposium
Experimental Caries in Rodents	Workshop
Screening of Antibacterial Compounds	Workshop with representatives of pharmaceutical industry

Detailed Program reports were given at the three regular meetings of the Dental Caries Program Advisory Committee and at the November 1973 meeting of the National Advisory Dental Research Council.

National Caries Program-sponsored publications during the year included:

"Streptococcus mutans and Dental Caries"
Proceedings of a roundtable discussion at the Annual Meeting of the American Society of Microbiologists.

"Physicochemical Mechanisms of Caries"
Proceedings of a symposium, published as a Supplement to the Journal of Dental Research.

The Program contracted with the American Dental Association to update and reissue the well-received compilation of abstracts, "Advances in Caries Research," first published in 1972.

The Associate Director, NCP, served as editor of the book, "Oral Health Through Prevention," to be published by the Fogarty International Center. The Associate Director and members of his office staff presented lectures and seminars on the Program at the University of Maryland School of Dentistry, U.S. Naval Dental School, U.S. Army Institute of Dental Research, State and Territorial Dental Health Officers, University of Alabama in Birmingham, University of Michigan and Columbia University.

Scientific Activities

In January 1973, the National Caries Program constructed a plan of action for its major strategies and objectives. Because this Program plan is easily comprehended and helps display an accurate picture of Program activities and directions, we employ it, almost as a matter of custom, as the framework for reports. We use it routinely for staff review of plans and progress, since it provides a simple but organized way in which to overview the twenty-odd strategy components in the Program.

At regular meetings, Program staff discuss the progress and review the urgency of achieving component objectives in each strategy, and attempt to identify individual projects that must be carried out to achieve these objectives. In addition, each project is assessed with regard to the best way of carrying it out, i.e., by grant, contract or by direct operation of our staff. This choice takes into consideration a number of factors including: (1) the exactness with which the objective of the research can be described, (2) available skills and facilities within our staff to carry out the investigation, (3) degree of innovative and exploratory skill that is desired, and (4) current NIH guidelines on choice of support mechanism. Grants are used as the mechanism whenever high quality proposals are available that match program needs. It should be emphasized that continued success of the Program depends greatly on the independent perspective and fresh concepts of scientists conceiving grant supported research. To assist communication among scientists, particularly when relevant areas of research lie in more than one specialty, frequent "state-of-the-art" workshops and published proceedings of these workshops are supported. To further facilitate communication of Program needs to scientists we have commenced using the NIH Guide to Grants and Contracts to disseminate staff summaries of areas where these seem to be unusual opportunities for research. These new "Requests for Applications" (RFA) for research grants are analogous to "Requests for Proposals" (RFP) for contracts.

In the management of grants the Caries Grant Programs Branch functions according to the policies and procedures of the NIH Extramural Programs. Thus, after study section review of new applications, staff of the CGPB presents those that are caries relevant to the NADRC for final recommendations. CGPB staff also periodically reviews for Council the activities and program plans of the Branch in relationship to the total activities and objectives of the National Caries Program.

Comprehensive planning, centralized in the Office of the Associate Director, but including advisory input from nongovernment consultants and scientists from other NIDR units, preceeds formulation of all requests to initiate contracts. These requests are submitted to the Office of Collaborative Research (OCR) which then advertises the requests through RFP's, administers an in-depth scientific review of responses using non-government expert panels, and negotiates the contract. Prior to award, each procurement is carefully reviewed by the NIDR Contracts Review Group. When implemented, each contract has an OCR contract specialist and an NCP project scientist who work closely with the contractor and principal investigator to see that project objectives are achieved. It should be emphasized that though contracts facilitate

reaching program objectives in a timely and efficient manner, their design, implementation, and monitoring necessitates very large expenditures of staff time. In FY 1974, the CGPB budget increased markedly due to the release of impounded FY 1973 funds, and due to revision in the President's FY 1974 budget. Expenditures for contracts decreased about 10 percent during the same period, and use of direct operations funds remained relatively constant.

	FY 73	FY 74
Grants		
Budget ($ million)	2.993	3.916
Number of funded research grants (Type 1, 2 & 5)	50	51
Total number of active research grants	59	62
Number of training grants	3	1
Number of fellowships	5	4
Number of research career development awards	3	3
Contracts and other procurements		
Budget ($ million)	3.00	2.60
Number of funded contracts	44	32
Total Number of contracts	50	53
Direct Operations		
Budget ($ million)	0.8	0.8
Number of projects	-	23

In the sections that follow, we review the progress that has been made in FY 1974 toward the overall goal of caries prevention in the United States. The review is organized according to the main Program strategies which are: (I) Combat the microbial agent, (II) Increase tooth resistance, (III) Modify the diet, and (IV) Develop improved delivery systems for caries prevention. Within each strategy area the review is organized according to strategy components and principle objectives are given at the beginning of each of these sections. Within each section are described all NCP activities--grants, contracts, direct operations, meetings with consultants, etc.--carried out during FY 1974 to meet those objectives. One major and crucially important activity is not apparent in this description and therefore should be noted before proceeding. The staff of the Biometry Section, Caries Research and Prevention Branch, through review of experimental design, statistical analyses, and actual data handling, is involved in the success of the majority of our direct operations and collaborative activities.

STRATEGY I: COMBAT THE MICROBIAL AGENT

Pathophysiology. National Caries Program strategy in this area is to achieve several major objectives:

1. Identify the species and strains of oral microorganisms chiefly responsible for the initiation of each of the major types of caries.

2. Determine the special aspects of metabolism of these microorganisms that impart cariogenicity.

The first of these objectives requires the isolation of specific strains of microorganisms that appear to be associated with caries initiation and the development of technics for simple identification and quantitation of these microorganisms. Progress toward this objective has been slow since transport media, dispersion technics and other methodologies that allow both high viable counts and easy identification of microorganisms in plaque samples have not been available. NCP scientists are working directly on these problems in our laboratories, and the Program is supporting similar activities through grants at Eastman Dental Center, Forsyth Dental Center, and several other institutions. At the University of Michigan, for example, a grantee has been comparing culture media for growth of oral Gram-positive bacteria. He finds that MM10 sucrose blood agar is an ideal culture medium for the isolation, nonselective enumeration and differential counting of these bacteria. To test this medium he has employed it for the enumeration of the bacteria in normal and disease-associated plaque samples less than 1 mg. in weight, removed from interproximal sites, and in samples picked up on the tip of dental explorers during routine use. Use of the technic showed that S. mutans was present in a high concentration on explorers used on carious teeth. Further studies have been initiated to establish whether this microorganism and caries can be spread through use of this common dental procedure.

An additional objective is development of improved technics for rapid enumeration of strains of S. mutans and other species in plaque samples. To develop fluorescent antibody reagents we have supported a one-year contract with Huntingdon Research Laboratories, and have an ongoing interagency agreement with the Center for Disease Control at Atlanta. The immediate goal is a set of highly purified reagents that work well even when considerably diluted and are specific for each of the strains of S. mutans, and for Actinomyces viscosus and naeslundii as well. The scientists at the CDC have discovered that by percolating crude antibody preparations through columns of cross-reactive bacteria that satisfactory amounts of specific, high-titer antibody can be prepared. Currently these reagents are being tested on plaque samples and smear preparations of known composition in a cooperative arrangement with NCP laboratory scientists.

To develop other identifying criteria, these scientists are employing numerical taxonomic and conventional methods to classify strains of S. mutans supplied by the American Type Culture Collection in Bethesda. In the coming year the contract with CDC will support the development of Fluorescent Antibody reagents for other bacteria, including Arachnia propionica and Odontomyces odontolyticus, believed to be involved in root caries and periodontal disease. In addition to progress achieved by these contractors, innovative new technics for identifying oral streptococci are being developed by grantees. At Forsyth, for example, scientists have developed a plating medium which allows identification of S. mutans when it is present only at very low levels in plaque samples and devised a color-forming reagent, highly specific for S. mutans colonies, that can be sprayed on agar plates. A further example of work being carried out to reach the objective of easy identification is a novel set of identifying reagents for S. sanguis based on sensitivity to and liberation of bacteriocins by this microorganism.

The second objective under Pathophysiology is to gain further information on metabolic features of cariogenic microorganisms, especially those features that are unique or that impart cariogenicity. This information, hopefully, will provide a base for design of growth inhibitory or caries blocking agents. Through direct operations, contracts and particularly grants, the NCP is providing major support in this area and studies range from biochemical problems such as the synthesis of extracellular polysaccharides, transport of nutrients through the cell wall, and function of extracellular proteolytic enzymes, to physiological processes of these microorganisms such as the response to intermittent food supply and anaerobiasis, symbiotic relationships within plaque, functions of bacteriophages, adhesion to surfaces, and reactions with salivary constituents. A few of these studies will be described briefly.

In the important area of extracellular activities of oral streptococci, a grantee at Villanova University is studying extracellular polysaccharide synthesis by S. mutans (FA1) and S. salivarius (SS2). He finds that the enzyme of the first microorganism has both dextransucrase and levansucrase activity, and apparently is a glycoprotein since it contains about 40 percent carbohydrate which is neither dextran nor levan. The enzyme of S. salivarius, on the other hand, exhibits only levansucrase activity. The product is highly branched. Since both of these enzyme preparations show multiple bands during gel electrophoresis it is possible that these preparations are mixtures of enzymes responsible for branched as well as linear products or that they are mixtures of protein subunits. At the University of California at San Francisco, a grantee has been extensively purifying the dextransucrase of S. sanguis (804). He reports finding 6 subunits with molecular weights in the range between 24,500 and 135,000 Daltons. This investigator also has been studying the mechanism of action of the enzyme and reports that when the glucose moiety of sucrose is incorporated into dextran it does not exist temporarily as free glucose. This provides one bit of evidence about the mechanism of this key reaction, but much additional research is urgently needed on questions such as whether more than one enzyme is required to make branched polysaccharides or whether glucose is "inserted" into the polymer chain or added to the chain at the end. If these and other questions

concerning the structure of the enzyme active site and reaction mechanism could be answered, it would create a valuable base of information for scientists attempting to find or synthesize an agent to block dextran production. Among the reasons hindering research to answer these questions are technical problems in preparing the enzyme free from attached product and, alternatively, in analyzing the heterogeneous product. Recently, however, applicants for grants have presented evidence that these problems can be solved, and research on the mechanism of these enzymes is commencing at the University of Miami, Ohio State University, and other institutions.

The NCP also is supporting research at several laboratories on the structure and properties of polysaccharides formed by these enzymes. At Stevens Institute of Technology at Hoboken, New Jersey, a physical chemist is studying the gross structure and properties of the levans of S. salivarius and A. viscosus. At the University of California at San Francisco, a scientist is continuing studies on polysaccharides isolated from human plaque and on their individual susceptibility to degradation by dextranases, and in NCP laboratories, staff scientists are carrying out assays with rats on the anticaries effectiveness of several new dextranases developed for us under contract with Beckman Instruments Company.

In the area of cellular, as opposed to extracellular, metabolism of cariogenic microorganisms, the NCP is supporting a number of projects primarily through grants. These studies are widely scattered at the Universities of Minnesota, Oklahoma, and Connecticut, and the Universities of Oregon and New Jersey Dental Schools, and the Medical College of Georgia. Some of these are straightforward biochemical studies on the mechanisms through which sugars and sugar alcohols enter the microorganism, on the intermediary metabolism of carbohydrates, on intracellular polysaccharide storage, and on the uptake and metabolic utilization by the microorganism of enamel phosphate. On the other hand, several studies combine genetics and biochemistry in a novel fashion. Cariogenic streptococci first are mutated to modify their cariogenicity. By comparing these mutants to normal microorganisms, the scientists plan to search for important changes in metabolic processes. It is hoped that this approach will identify unique cariogenic features of these microorganisms and point to good targets for development of anticaries agents.

In the area of physiological aspects of etiology, NCP is supporting a large program project at Forsyth Dental Center plus regular project grants at Forsyth, Eastman Dental Center, Temple University, Massachusetts Institute of Technology, and Northwestern University. The program project has as its principal focus the process of plaque development and the mechanisms for adhesion of plaque microorganisms to each other, to plaque matrix material and to the pellicle covered surface of the teeth. It is reported that there appears to be a sharp "cut-off" in salivary concentration for each species below which none of that species adheres to the teeth. Since S. mutans binds rather firmly to teeth and plaque, it can be visualized that generally the concentration of this species in saliva will be too low for colonization of fresh tooth surfaces or for transmission or implantation in a new host. On the other hand, one may speculate that with frequent exposure to nutrients, S. mutans and other plaque formers spread laterally from small foci of infection. At Forsyth both the

dextran dependent binding of S. mutans to the pellicle surface, the inhibition of this process by salivary immunoglobulins, the saliva dependent binding of S. sanguis and S. mitis to the plaque matrix and the possibility of eliminating oral foci of infection as a basis for caries control are under intense study.

At Eastman Dental Center a grantee is studying the types and amounts of acid produced by plaque at the interproximal contact point between teeth. This is one of the most active caries sites in adolescents, but is extremely difficult to study due to small plaque samples that can be obtained from it. The Eastman investigator is using gas chromatography and micro-titration technics. She finds after an oral sucrose rinse that this plaque is generating copious amounts of formic as well as lactic acid. At Temple University and the Massachusetts Institute of Technology grantees are studying the adaptation of microorganisms to the unusual conditions within plaque--low oxygen potential and frequent periods of low nutrient supply. Under such conditions, particularly when there is nitrogen starvation, streptococci respond by becoming thicker walled and more resistant to many drugs. The investigator at Temple University is studying the phenomenon of increased drug resistance in plaque streptococci, the group at MIT, using continuous culture technics is examining short-term responses of oral streptococci to rapid changes in nutrients mimicking conditions in the mouth, and a scientist at the University of Miami is determining the amino acid requirements of these bacteria relative to levels available in the saliva.

Epidemiology. Program strategy in this area is to achieve the following major objectives:

1. Gain information that will assist in setting Program priorities through studies on disease prevalence.

2. Gain evidence on cariogenicity and transmissability of microorganisms through studies on association with disease and through direct experiments.

3. Obtain information that could lead to new methods of disease control by establishing how environmental factors affect caries prevalence.

Epidemiologic studies followed by animal trials have led to the implication of S. mutans in smooth surface caries and to the concept that transmission of S. mutans, either between individuals or between sites within the mouth does not readily occur. To establish when S. mutans first appears in the oral cavity NCP scientists currently are conducting studies on rats and on young children.

In addition to information on transmissability, further information is needed on the relative cariogenicity of S. mutans serotypes and other microorganisms that cause or contribute to caries at various sites on teeth. It is interesting that scientists who before used mixed samples from the entire dentition in epidemiologic studies now intend, through use of microtechnics, to narrow the focus of study to microbiota at specific single sites on the teeth of

children. Through this approach they hope to be able to establish which species are present immediately before a lesion first appears. To conduct studies on microbial changes at single sites or to carry out classical epidemiologic studies on group-related prevalence of specific microorganisms, one requirement is simple methods of microbial identification and enumeration as described in the previous section. For studies on prevalence in groups one also needs populations with high and low levels of caries and other characteristics such as low mobility, uniform diet, and lack of dental treatment. Such characteristics, in the main, are found only in isolated primitive settings. In Papua-New Guinea we are supporting a study through contract with the World Health Organization on tribes having similar diets but highly dissimilar caries prevalence. The WHO team, in an attempt to capitalize on the unusual possibilities presented by this population to develop new information about caries etiology, is collecting information on dependent variables such as mandibular arch dimension and salivary viscosity in addition to caries prevalence data. It is hoped that in-depth analysis of these data will reveal synergistic and dependent effects among variables, lead to new clues about caries etiology, and suggest technics for caries control. Much of this work still is in the analytical stage; however, the contractor reports that differences in numbers of oral microorganisms, levels in strontium in enamel, and combinations of these factors are strongly associated with the prevalence of caries. In Colombia, South America, a Forsyth Dental Center epidemiologist studied two isolated villages, Helonconia and Don Matias, which appear highly similar except for caries rates of 5.5 and 13.9 DMF teeth, respectively. This scientist recently reported that in examining early analytical results he sees two differences between the towns. One difference is a strong positive correlation between levels of manganese in soil, water and teeth and dental caries, and the other a negative correlation to water hardness, expressed as levels of calcium and magnesium. Samples of water from these towns have been brought to our laboratories to see if their trace metal content is in some way related to plaque metabolism.

In the Papua-New Guinea study, root caries was found to be quite extensive. In civilized countries, also, root caries apparently is highly prevalent, but the exact dimensions of the disease and the cost of treatment and restoration have not been determined. To provide a rational basis for deciding the extent of resources to be invested in this area, relative to other types of caries, the NCP contracted with Temple University to carry out root caries prevalence studies in several populations. In this study freshly extracted teeth, full mouth X-rays, and individual patients were examined for evidence of the disease. Lesions on roots were reported as caries only when softened or broken-down tooth substance was clearly demonstrable. The prevalence of lesions was found to be quite age dependent, but it was typical that about one-third of the people examined had root caries on one or more teeth. Independent assessments that arrived at similar findings on prevalence of the disease have been carried out by NCP staff in cooperation with the U.S. Coast Guard and Department of the Army.

Management of root surface caries is generally conceded to be difficult and expensive, so ways must be found to prevent the disease, possibly through immunization. A logical first step is to learn more about the etiology of

the disease and, in particular, the identity of the microorganisms that cause it. Part of the activities of the large NCP program project grant at Forsyth is devoted to root caries etiology. Scientists supported by this grant recently reported that on the root surface lesion S. mutans is a predominant organism along with S. sanguis, S. mitis, other streptococci with characteristics of enterococci and filamentous microorganisms typical of the genus Actinomyces. At the advancing front of the lesion deep within the cementum almost pure cultures of an aerobic diptheroid were isolated. These microorganisms did not ferment glucose, but were proteolytic and strongly resembled Arthrobacter. It is interesting that at the advancing front of coronal caries one usually finds that the bacteria are Gram-positive short rods similar to lactobacilli.

At the University of Michigan a grantee reports that two types of root caries plaque can be distinguished on the basis of presence or absence of S. mutans. The first type, comprising two-thirds of the samples, had the following average composition: S. mutans, 30%; A. viscosus, 47%; S. sanguis, 1%; Veillonella, 4%; and other strep. 18%. In the other plaques it was unusual to find S. mutans, and the average composition was S. sanguis, 48%; A. viscosus, 41%; Veillonella sp., 2%, and other streptococci, 9%.

Antimicrobials; Antiplaque agents. In this area NCP strategy is to achieve the following objectives:

1. Identify antibiotic or chemical agents that will inhibit the growth or adhesion of cariogenic bacteria and plaque or prevent acid formation on the tooth.

2. Develop comparative testing arrangements that will help manufacturers to develop such products with standard assays of antimicrobial, antiplaque and anticaries activity.

The first sections of this report dealt with "basic" research to find out more about the initiation of the carious lesion; this section is the first of several in which the activities outlined represent systematic attempts to use the basic information to develop control measures for the disease. A good example of this process began a few years ago with the salient observation that extracellular glucans formed from sucrose facilitate adhesion on smooth surfaces by S. mutans. Since then, with considerable support from NCP, scientists have been seeking ways to interfere with glucan-based adhesion. One approach used by a grantee at the University of California is to find nontoxic analogs of sucrose that would block the enzyme, dextransucrase. The scientist has synthesized or isolated a number of novel sugars, recent ones being isosucrose, 1-kestose, lactulosucrose and planteose. He reports that despite their similarity to sucrose most of these analogs do not interfere with glucan formation. Maltose, a glucose-glucose analog of sucrose, however, does show definite ability to inhibit dextransucrase.

Another approach to plaque control would be through use of agents that hydrolyze glucans or that split the bond between glucans and the microorganism or between glucans and the tooth surface. To expedite research in this area, NCP

has contracted with the University of Minnesota to develop a simple assay for bacterial adhesion. The assay now appears to be quite reliable, and its developer is using it in a project to isolate and identify the components of the cell wall of S. sanguis that are involved in binding. In NCP laboratories work continues on the testing of enzymes that hydrolyze glucans and that alone or in combination with other enzymes such as proteinases could effectively hydrolyze human dental plaque. Over the past year these scientists have been carrying out animal trials of several dextranases prepared through a contract with Beckman Instruments Company. One of these enzymes with strong activity against branched glucans exhibits potent antiplaque properties when supplied continuously in drinking water, and now is being tested as a diet additive.

With many anticaries chemotherapeutic regimens, effectiveness presumably depends on the agent being present for prolonged periods in the mouth. Consequently, the Program has been looking closely at technics for prolonged slow release or activation of agents from small repositories in the mouth. Recently, the NCP initiated two contracts, one with Southern Research Institute, Birmingham, Alabama, and the other with Polysciences, Inc., of Warrington, Pennsylvania, for development and evaluation of oral systems for slow release of fluoride. In addition, NCP laboratory scientists and a grantee at Tufts University School of Dentistry are trying to modify 8-hydroxyquinolines and bis-biguanides, two families of promising antiplaque agents, to make them adhere longer to the tooth pellicle surface.

The NCP is exploring the use of chemotherapeutics for caries control with considerable caution since the prolonged use of these agents does carry potential for toxic reactions, sensitization of oral tissue, and development of resistant microbial strains. An initial NCP venture into this area was a contract with the Royal Dental College, Aarhus, Denmark, for a closely controlled study of long-term twice daily use of chlorhexidine. Final reports on this study have been received and indicate that prolonged use of such chemotherapeutics is feasible and effective against plaque. A similar report of insignificant adverse reactions and minimal tendency to induce resistant strains has been received from a grant-supported, year-long clinical trial of the antibiotic, Kanamycin, at the University of Michigan. This trial was carried out to explore the feasibility of using 5-day periods of intensive therapy with Kanamycin paste alternating with 5-week periods without treatment, and was found successful in controlling plaque in institutionalized children who could not brush their teeth.

Interest has increased in the last few years in the possibility that fluoride may have an antimicrobial effect as well as an effect on the acid solubility of enamel. To test this possibility directly, a grantee at Ohio State University has developed a stable mutant of S. mutans Strain 6715 that exhibits good growth in media containing fluoride at levels up to 600 ppm. When this mutant was tested in gnotobiotic rats, it was found that customary low levels of fluoride still markedly protected the teeth from caries, thus suggesting that the effect of fluoride is on enamel. One may speculate, however, that this result also could occur if in the mutant an essential factor in microbial cariogenicity remained fluoride-sensitive, even though microbial growth and other parameters became largely fluoride insensitive. To examine this

possibility, a collaborative project between the Ohio State University grantee and NCP scientists is now underway to examine the mutant exhaustively.

Other than those just mentioned, there have been relatively few well-controlled clinical trials of plaque control based on chemotherapeutics and antimicrobials. Nevertheless, on the laboratory shelves of pharmaceutical companies, there are numerous compounds among which it is highly likely there are some with ideal properties for caries prevention. The NCP is attempting to encourage the identification and development of these compounds by offering two stages of free, standardized screening with feedback of information to the company on all test results. The first screen conducted under contract at the Medical College of Georgia involves *in vitro* assays for inhibition of growth, plaque, and acid production by cariogenic microorganisms, and *in vivo* assays in rats for inhibition of caries and possible toxic manifestations. In the two years that this pre-clinical testing service has been in operation, 70 compounds have been assayed representing products of 15 pharmaceutical companies. Twelve of these compounds have properties which definitely appear to merit further testing. The second screening carried out under contract with Forsyth Dental Center provides a standardized short-term clinical trial of antiplaque and antigingivitis activity of agents that have received necessary clearance from the Food and Drug Administration. This service has been available for only a short period.

Immunization: In this area NCP strategy is to achieve the following objectives:

1. Determine the action of secretory antibodies on the bacterial content and function of dental plaque.

2. Identify substances capable of eliciting high and prolonged oral antibody titers against cariogenic microorganisms.

3. Determine efficacious sites of immunization and study responses of lymphatic, salivary and other tissues to immunization.

4. Identify and elucidate caries protective mechanisms of saliva in addition to secretory antibodies.

During FY 1974, there were marked increases in evidence accumulated by NCP and other groups supporting the concept that immunoglobulins present in the oral cavity provide natural defense against cariogenic microorganisms. Evidence also has increased supporting the possibility that this defense mechanism could be amplified to provide effective caries control through vaccination. The NCP is supporting studies both to obtain preliminary data on the feasibility of this approach and to obtain basic information on the mechanisms of secretory immunoglobulin synthesis and function.

At the University of Alabama two grantees are probing basic phenomena of oral responses to antigenic materials. One of these scientists is systematically studying immune responses to specific cariogenic and noncariogenic microorganisms with emphasis on possible adjuvant effects caused by preinfection with organisms like *Cl. difficile*. Levels and classes of immunoglobulins

both in serum and saliva and the morphology of lymph nodes and spleen are being carefully examined. Another scientist at the University of Alabama is demonstrating by use of immunofluorescence technics that resistance factors found in saliva are not only present in plaque but accumulated there in high concentration, possibly providing protection against caries. At New York University a grantee is studying the oral and gastrointestinal routes by which antigens of cariogenic microorganisms naturally come in contact with antibody forming cells. This information is important to eventual routes and technics for human vaccination.

In the more applied area of the Program, contracts are being used to obtain information on which antigens of cariogenic microorganisms are the best for developing a useful caries vaccine. Some of the questions needing resolution are: (1) which of the several extracellular enzymes or cell wall components will provide the most powerful antibody response, (2) whether antigen of a single S. mutans strain will be adequate for immunization, or whether a mixture of species and strains will be required, and (3) whether there are any pathological responses to use of these preparations. Among the antigenic preparations under study are S. mutans killed whole cells and cell fractions and S. mutans enzymes such as dextransucrase, levansucrase, and glycosidic hydrolase. The extracellular enzymes are relatively easy to prepare, but each in actuality comprises a small family of enzymes which some scientists feel must be purified further. After immunization of rats, hamsters or monkeys with these preparations, scientists measure induced level of salivary and serum antibody, in vitro capacity of antibody preparations to inhibit the enzyme or inhibit S. mutans growth or adhesion to surface, and caries resisance in immunized and sham vaccinated animals. These types of studies are being supported through contract at Southern Illinois University and Forsyth Dental Center, with supportive studies being carried out in NCP laboratories. In addition, the NCP has initiated a contract with Hazleton Laboratories, Inc. to establish a nearby monkey colony to facilitate testing of immunogens. Among the promising preparations that will be tested are several dextransucrase preparations that have been highly purified by NIDR intramural scientists.

In addition to investigations specifically on secretory immunoglobulins, the NCP is attempting to stimulate increased research on suspected natural defense mechanisms involving salivary enzymes such as lysozyme, peroxidase or lactoferrin or mechanisms involving leucocytes. These mechanisms may operate independently or in conjunction with immunoglobulins. To increase research in this area, the NCP Caries Grant Programs Branch recently issued an announcement in the widely circulated NIH Guide solicitng research grant applications for study of these highly relevant phenomena.

STRATEGY II: INCREASE TOOTH RESISTANCE

Topical Fluoride and School Water Fluoridation: In this area NCP strategy is to achieve the following major objectives:

1. Distinguish and elucidate fluoride's systemic, topical, smooth surface, sulcal, biological, and mineralization effects

2. Determine which fluoride compounds, vehicles and frequencies of application to teeth are most effective in preventing caries

3. Establish optimum concentrations of fluoride to be used for school water fluoridation in relation to water consumption in different geographic areas.

Use of fluoride continues to be the most effective, currently available method for caries control. It is likely that this agent in several formulations will be the basis for caries control regimens recommended by the NCP for use by many millions of children and adults. For this reason the NCP continues to commit major portions of its resources to obtain complete information on how fluoride prevents caries, and to obtain comparable data on effectiveness of available fluoride combinations and treatments.

During FY 1974, NCP scientists have become increasingly involved in testing the various hypotheses suggested to explain the mechanism caries inhibition by fluoride. In one set of experiments carried out with a collaborator at the University of Maryland, fluoride was tube-fed to rats during the period of pre-eruptive growth so that any tooth solubility effects would be restricted in the main to the result of systemic fluoride. It was found in these experiments that systemically incorporated fluoride did not change the amount of calcium that known cariogenic microorganisms release from the tooth surface, but apparently did affect the amount that collects in plaque on the tooth surface. In another series of experiments NCP scientists have been attempting to distinguish the mechanisms of caries inhibition at low exposures to fluoride such as in municipally fluoridated water from those achieved by intensive treatment of the tooth with topically applied fluoride. In experiments in our laboratories in which rats were continuously provided drinking water containing only 10 ppm fluoride, marked protection against caries was found, but no measurable increase in tooth enamel fluoride was detected. On the other hand, by providing rats with high levels of fluoride (up to 150 ppm) for a short period early in life, a second type of protection was discerned in which there is caries protection that varied with the level of enamel surface fluoride. The two treatments were found to be additive in effect and capable of providing nearly total protection against caries.

To test the comparative benefits of these types of fluoride treatment in humans, the NCP recently initiated contracts with the University of Oregon and Forsyth Dental Center to conduct 3-year clinical trials of short-term intensive treatment to build high levels of fluoride into the surface layers of enamel in comparison with long-term treatment with small amounts of fluoride

supplied daily. In addition, the two contracts to develop technics for slow intra-oral release of fluoride are part of NCP's efforts to possibly develop a combination regimen based on several fluoride protective actions.

A number of enamel sampling technics have been developed independently for determination of enamel fluoride concentrations. These technics have not been compared nor calibrated critically through wet chemistry analysis of bulk enamel. In addition, these technics are inadequate for detailed examination of mechanisms of protection by fluoride since they do not reveal the chemical combination or physical location of the fluoride in the microstructure of enamel. To eliminate some of the uncertainty in use of these methods, the Program has entered into contracts with the American Dental Association and the University of Iowa for a quantitative comparison of the reliability, validity and precision of the acid etch and mechanical abrasion methods of enamel fluoride biopsy and analysis.

A number of topical fluoride agents such as acidulated phosphate fluoride, stannous fluoride, ammonium fluoride and amine fluorides have been tested and found effective in practice. Since the chemistry of the reactions of these agents with hydroxyapatite is not completely understood, research in this area has attracted the attention of several inorganic and physical chemists. A grantee at the University of Minnesota believes that, simply on the basis of chemical mass action, several of these agents are incorrectly formulated and to improve them has set about a thorough examination of the amounts of CaF_2, $Sn_3F_3PO_4$ and fluorapatite formed under various conditions of acidity and phosphate concentration. Two other grantees, one a physical chemist at Cornell College in Iowa and the other a dental scientist at the University of Missouri in Kansas City, are collaborating in the studies on the in situ reaction of SnF_2 with tooth enamel. They report that they find no evidence of fluorapatite formation and suggest that $Sn_3F_3PO_4$ formation explains the anti-caries activity of SnF_2.

The Program has urgent needs for information on the relative merits of these agents for caries control for school-age children, and therefore has entered into a number of contracts for side-by-side 3-year clinical trials of pairs of topical agents. At Forsyth Dental Center ammonium fluoride is being compared with sodium fluoride. Twice-yearly topical treatment and daily mouth-rinsing also are being compared in these studies. After one year of treatment the data indicate that daily rinsing may be slightly better than twice-yearly topical treatment and indicate that, even though resulting enamel fluoride concentrations are higher, ammonium fluoride does not provide improved caries protection relative to sodium fluoride.

At the University of Miami, a commercially available amine fluoride is being compared to acidulated sodium fluoride. In this study the agents are applied as gels, using close-fitting mouthpieces. Final clinical examinations in this three-year study will take place in late 1974. Through a contract with the Florida Department of Health, a comparison is being made of use of a mouth-rinse and dentifrice based on an amine fluoride and a similar mouthrinse and dentifrice based on inorganic fluorides. This study, involving approximately 2100 children 11-12 years old, will conclude in 1975.

Another fluoride compound that has been studied for several years at Eastman Dental Center as a potential agent is titanium tetrafluoride. Laboratory evidence shows that fluoride in this combination adheres exceptionally strongly to tooth enamel. The NCP recently has contracted with the University of Michigan to conduct a controlled clinical trial of this agent.

NCP staff also are continuing long-term field evaluations of several preventive regimens for school children that are exceptionally attractive with regard to cost and ease of program implementation. Three collaborative projects with the North Carolina State Board of Health are being conducted to find a delivery system at school to compensate for negligible levels of fluoride in home water supplies. The first of these, a 12-year study initiated in 1968, evaluates fluoridation of the school water supply. The second, an 8-year study started in 1969, evaluates chewing and swallowing daily acidulated phosphate-fluoride (APF) tablets. The third, again a 12-year study, was initiated late in 1972, and is based on a combination of school water fluoridation and weekly mouth-rinsing with sodium fluoride solution. Interim results show a protection against caries of the order of 45 percent. In addition to these projects in North Carolina, a collaborative study is being carried out with the Virginia Department of Health to evaluate a combination of treatments: daily APF tablets, weekly sodium fluoride rinsing, home use of a fluoride dentifrice and oral health education in the schools. This program will continue until 1984.

Adhesive Sealants: In this area, NCP strategy is to achieve the following major objectives:

1. Evaluate adhesive sealants with respect to average duration of retention, caries protection and cost when used in public health programs

2. Determine result of sealing over incipient caries lesions

3. Obtain information on pellicle and enamel surface properties which affect or are affected by sealant application.

The NCP currently is focusing attention on the ultra-violet light catalyzed bisphenol A sealant developed at the Eastman Dental Center. Three field trials of this sealant were initiated in 1970-71, to determine duration of retention of the sealant, effectiveness in inhibiting dental caries, time involved and cost of applying the sealant, and incidence of new lesions at sites where sealant has been lost. NCP staff are directly involved in one of these studies, a clinical trial involving 700 children in Kalispell, Montana which has low levels of fluoride in its water supply. The other two studies are being carried out by means of contracts and involve 2000 children in Rochester, New York, a fluoridated community (Health Research, Inc.), and 2700 children in the Virgin Islands (University of Puerto Rico). Results of these studies currently are being prepared for simultaneous publication late in 1974.

In addition, we have awarded a grant to Eastman Dental Center for an investigation of the results of sealing over viable organisms in occlusal pits and fissures and early carious lesions. If it should be established that there is little danger due to continued microbial activity under the sealant, then involvement of dentists in checking teeth and repairing small lesions prior to applying sealant could be markedly reduced.

The Program also has awarded several grants for research on the structure and composition of the enamel surface that hopefully will lead to development of sealants that adhere strongly to unetched enamel and that resist leakage. Scientists at the University of California at Berkeley, Columbia University, Duke University and Forsyth Dental Center are employing a variety of advanced laboratory technics to study dimensions of pores in enamel, electric charges within pores, and penetration of various agents into enamel. One of these technics involves use of spherical and ellipsoidal molecules that slip into porous materials and through electron spin resonance technics can be made to transmit information on the environment within the capillaries.

Inherent Resistance: In this area NCP strategy is to achieve the following major objective:

1. Define factors involved in formation and maturation of enamel which may influence susceptibility to caries.

The grant-supported research previously described is concerned with bulk properties of enamel. However, one of the salient observations made at the Symposium on Physicochemical Mechanisms of Dental Caries (June 1973, Airlie House, Virginia) is that composition of enamel with regard to protein, carbonate and mineral elements varies considerably from place to place on the tooth surface. There is little information concerning possible relationships between enamel composition and focal susceptibility to carious attack. To obtain information on morphological characteristics of the enamel surface, a grant has been awarded to the University of Virginia where a materials scientist is using electron optical technics to study both the intact surface and the surface subsequent to early stages of carious attack. Parallel studies on chemical composition of caries susceptible sites are needed.

The Program also is supporting studies on acid resistance of hydroxyapatite crystals in enamel, substituted crystals grown in the laboratory and actual crystals separated from enamel and studied in bulk suspensions. At Case Western Reserve University a grantee reports that though calcium chelation as opposed to acid solubilization has been suggested as the basis for enamel destruction, the appearance of apatite crystallites from natural white spot enamel resembles that obtained by *in vitro* etching with acid rather than chelating agents. Grantees at New York University and the University of Michigan are growing hydroxyapatite crystals containing trace elements found naturally in teeth and studying these with respect to stability. A grantee at the University of California School of Dentistry is carrying out *in vitro* studies on actual crystallites. He reports intriguing differences between

sodium and potassium ions in potentiating crystallite degradation by citrate and suggests that the high levels of sodium found in bone may have an important bone stabilizing function.

STRATEGY III: MODIFY THE DIET

Sucrose Substitutes, Diet Supplementation and Diet Modification: In this area NCP strategy is to achieve the following major objectives:

1. Identify noncariogenic sweetening agents for use in manufacture of taste-competitive sweet snack and dessert foods

2. Investigate methods for supplementing and modifying foods to reduce plaque acid production or increase their buffering and other tooth protective effects

3. Establish and define effects of trace elements in food and water on caries experience.

An advisory workshop was convened in September 1973, to review data being generated by contracted studies on food cariogenicity being carried out at Eastman Dental Center, Harvard School of Dental Medicine and the University of Alabama. A consistent result in these studies was that the caries rate remained relatively high when sucrose was replaced by other simple carbohydrates. Though these results were obtained through short-term trials with rats, they do suggest that substitution of other sweet carbohydrates for sucrose will not be an effective caries control measure for humans.

As a means for possible testing of this postulate, the Program has contracted with the Institute for Technological Investigations in Colombia, South America, to produce a panella preparation (a cane sugar confection supplying all sucrose for isolated villages) in which sucrose is replaced by glucose and fructose. In the meantime, the NCP is redeploying its resources to develop noncarbohydrate sweetening agents, promote decreased consumption of all simple carbohydrates, and develop agents that added to high-carbohydrate foods would decrease their cariogenic potential.

Currently there is considerable commercial interest in and support of research on sweeteners. The NCP has thus far involved itself in this area only to the extent of contracting with the University of Pennsylvania for the isolation and characterization of an intensely sweet protein, "monellin." Properties of this sweetener hold promise for commercial application, and further evaluation and development probably will be taken over by food processing companies.

The Program during FY 1974 has been supporting a number of grants and contracts to assess the feasibility of decreasing the cariogenicity of foods through additives such as trimetaphosphate, calcium glycerol phosphate, and sodium phytate. At the Harvard School of Dental Medicine and at the University

of Alabama scientists supported through contracts had previously confirmed that low levels of trimetaphosphate are highly effective in protecting rats against the caries challenge of high sucrose diets. Another scientist supported through contract at the University of Alabama has shown that briefly dipping enamel slabs into solutions of either trimetaphosphate or fluoride provide similar high levels of protection in a human intra-oral test. On the other hand, a clinical trial contracted at the University of Alabama has failed to demonstrate an unequivocal anticaries effect by trimetaphosphate. A possible explanation of the results of this study is that incorporated in a sugar-based chewing gum, trimetaphosphate did block the cariogenic challenge caused by chewing the gum six times a day, but was at a level too low to decrease the caries-causing potential of the remainder of the diet.

The Program also has contracted with the University of Minnesota for a study of trimetaphosphate using student volunteers on controlled high-sucrose diets. Early results from this study show that at 5 grams per day this agent causes a marked reduction in plaque streptococci.

To avoid problems inherent in human trials, the Program has contracted with the Royal College of Surgeons in London for a study to establish whether it is feasible to obtain reliable data on caries using monkeys as the animal model; changes in plaque flora rather than occurrence of carious lesions as the measured parameter. This study, carried out by the Department of Dental Science tested phytate added to sucrose snacks and revealed changes in oral microflora in a short period of time, demonstrating the promise of this approach.

The NCP has recently contracted with the University of California to conduct a 2-month clinical trial in children of the cariostatic potential of a mouth-rinse containing calcium glycerol phosphate. The parameter measured will be changes in the chemical composition and development of plaque. This project is designed to confirm reports that this agent is cariostatic according to European clinical trials.

Dietary Trace Elements: In this area, NCP strategy is to:

1. Establish and define effects of trace elements consumed in food and water on caries experience.

In the earlier section on Epidemiology, studies in Papua-New Guinea were described in which increased levels of strontium in tooth enamel and increased levels of alkaline earth elements in local soils were found to be associated with low levels of caries. Studies in Colombia, South America also were described in which manganese in soil, water and tooth samples was found to be associated with high levels of caries.

Additionally, the Program has contracted for a study at Eastman Dental Center of the trace element content of enamel of teeth collected in the United States from areas of high and low caries incidence. Partial data from this study reveal that strontium as well as fluoride is found in low-caries areas such as

South Carolina. Conversely, boron and molybdenum are high in teeth from high-caries areas in New England.

Recently the Program awarded a grant to the University of Oregon Dental School for a project designed to reveal interactions between selenium and fluoride. This research was prompted by reports from epidemiological studies carried out in the middle 1960's that selenium in locally- produced foods in Oregon, Wyoming, Montana and South Dakota seems to counteract the benefit of fluoride in the water supply.

STRATEGY IV: DEVELOP IMPROVED DELIVERY SYSTEMS FOR CARIES PREVENTION

Cost/Benefit Analyses: National Caries Program strategy in this area is to achieve several major objectives:

1. Determine cost/benefit ratios of different preventive procedures in terms of teeth saved from caries

2. Establish the extent to which preventive procedures must be modified according to personal or community liability to caries, and relate these to cost factors.

As described above, the NCP at the present time is investigating the feasibility of developing a broad spectrum of control measures for dental caries. In some cases the users of these control measures will be children; in other cases they will be adults or elderly people. These age differences will be associated with different types of disease (e.g., occlusal, smooth surface, interproximal and root caries), and will dictate differences in preventive programs. Some of the consumers will live in cities, some in small towns, and some in rural areas. For each of these situations certain caries control measures or combinations of control measures may be more effective than others, may be better accepted, or will cost less or be easier to implement as local programs. As control measures are tested for effectiveness it is essential that all of the above factors be evaluated also, and it is also clear that prudent Program investment in preventive procedures will depend on analysis of a complex body of data. During FY 1974 NCP staff has met several times with consultants to establish further needs for data and data handling technics in this area, particularly the use of stochastic models to predict long-term societal impact of alternative approaches to community caries prevention programs.

To obtain fundamental cost-effectiveness data the Program has included a requirement for such analyses in several of its procurements. The costs of preparing tooth surfaces and applying sealant relative to caries reduction are being determined in Rochester, New York, under contract with Health Research, Inc., and costs and benefits of a program using both sealants and topical fluoride application in a low fluoride area are being determined on a Navajo Reservation in a study carried out through an interagency agreement with the Indian Health Service.

The NCP also is supporting two large contracts to demonstrate the total benefit achievable for school-age children when two further measures, sealants and topical fluoride treatment, are added to a conventional program of municipally fluoridated water, dental hygiene instruction and restorative care. These projects involving 1200 children at Ypsilanti, Michigan (University of Michigan), and 1500 children at Buffalo, New York (State University of New York), were initiated in 1972, and will continue into 1975.

These studies will provide data on the level of caries protection that can be achieved by combined procedures. However, it is also important to obtain comparable data on the cost-effectiveness of each available procedure by itself. To obtain this information, the Program recently initiated a contract with the University of Connecticut for a research study whereby the cost and effect of a topical fluoride application, pit and fissure sealant application, and supervised mouthrinsing with a fluoride solution are assessed singly and in combination.

Motivation and Acceptance: National Caries Program strategy in this area is to achieve the following major objectives:

1. Determine what personal or other factors are involved in motivating individuals and communities to adopt and continue to use caries preventive procedures.

2. Increase awareness among community public health personnel of the availability and highly desirable features of currently developed caries preventive measures.

An eighteen-month contract with the American Dental Association was initiated to assess the knowledge, beliefs, attitudes and current activities of practicing dentists relative to procedures for prevention of dental caries. The resulting survey, using a probability sample representative of U.S. dentists, achieved a response rate of nearly 90 percent, and revealed an overwhelming endorsement by dentists of caries prevention programs, including those which might be initiated in schools. The American Dental Association also is evaluating the potential of the current dental practice system for participation in a comprehensive caries prevention program for children, and is designing a study to determine the effectiveness of the dentist, singly and as a member of professional dental societies, in changing public attitudes relative to caries preventive measures.

Also, the Program has awarded a grant to the University of Connecticut for a study of children's acceptance of caries prevention procedures. This 3-year study will focus on: (1) the acceptance of new preventive procedures by the population, specifically related to new dental procedures, but generalizable to procedures in medical practice as well, (2) the response of children to procedures directed toward changing behavior regarding oral hygiene, (3) the characteristics of children relative to their response, and (4) the kinds of social support systems of families relative to their children's response.

In the project at the State University of New York at Buffalo, described in the previous section, one group of children in a combined preventive study receive a "behavioral motivation" program. This program includes instruction in oral hygiene with repeated reinforcement by hygienists and school teachers, motivation through the family, and encouragement to seek oral health care by means of educational meetings with participating staff.

Methodology of Early Caries Detection: National Caries Program strategy in this area is to achieve the following major objectives:

1. Develop and validate methods to diagnose caries reliably at very early stages

2. Identify characteristics of individuals which are highly predictive of caries susceptibility.

There continue to be a number of research questions such as the relative cariogenicity of sugars or of snack foods that cannot be studied in humans without the possibility of tooth damage. In clinical studies of anticaries agents, criticism even has been raised about the use of untreated control groups. To obviate these problems in designing experiments to provide unambiguous data on caries control, the NCP is investing considerable program resources in the area of early caries detection. If pre-carious changes in plaque or reversible "lesions" of the tooth can be reliably detected, these rather than clinical caries, could be used as the dependent variable in clinical trials. This capability also would appreciably shorten such trials and, in the dental office, could provide a basis for detection and treatment of vulnerable tooth surfaces before development of frank lesions.

In FY 1973, a contract was awarded to Gulf South Research Institute in New Orleans to develop a penetrating fluorescent dye diagnostic system for early detection of sub-surface demineralization. Several dye-penetrant combinations have been developed and shown by the contractor to improve markedly the ability of clinicians to detect artificial lesions on extracted teeth. The technic now is being tested in clinical trials to establish if "lesions" detected with its aid are truly pre-carious.

Through a contract with the University of Minnesota, an oral biologist is studying the microflora and biochemical characteristics of plaque in children in an attempt to discern changes correlated to the onset of carious lesions. At the University of Iowa a grantee is carrying out a longitudinal comparison of suggested caries susceptibility tests to establish if any have high caries predictive capability.

PART III

NATIONAL INSTITUTE OF DENTAL RESEARCH

ANNUAL REPORT

EXTRAMURAL PROGRAMS

July 1, 1973 - June 30, 1974

Edited By

Special Assistant for Program Coordination

Extramural Programs

Compiled By

Dental Research Data Officer

National Institute of Dental Research

National Institutes of Health

Bethesda, Maryland

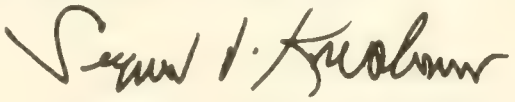
PREFACE

The NIDR Annual Report is intended to capture in printed form the essence of the Institute's total activities during the course of one fiscal year. The present format has evolved from our desire to make the Report more palatable to the reader, a better reference tool for its users, and less burdensome in preparation for its contributors.

A major change in compilation has been made in this issue to accommodate our several uses of the completed document. The Report for FY 1974 has been prepared in organizationally distinctive Parts to facilitate selective distribution to those who are concerned with or require as a working instrument less than the total publication. These are: Part I, Office of the Director, Research Projects and Indexes; Part II, National Caries Program; Part III, Extramural Programs; Part IV, Intramural Research; and Part V, Contracts.

For the third year, we have continued the practice of using a modified SSIE Notice of Research Project form (PHS 166) for the Individual Project Report. These are collected together as a section of Part I. This section, on blue paper, is accompanied by a number of indexes, for ease of retrieval and analysis, and a Classification Guide to Subjects and Categories.

We apologize in advance for any errors that may have escaped our attention and would appreciate your comments and suggestions so that we may continue to improve this document in the future.



Seymour J. Kreshover, D.D.S., M.D.
Director
NIDR

CONTENTS

PART I - OFFICE OF THE DIRECTOR

PART I - RESEARCH PROJECTS AND INDEXES

PART II - NATIONAL CARIES PROGRAM

PART III - EXTRAMURAL PROGRAMS PAGE

Report of the Associate Director 1

Periodontal and Soft Tissue Diseases Program 19

Craniofacial Anomalies Program 41

Restorative Materials Program 59

Mineralization, Salivary Secretions and Nutrition Program 67

Pain Control and Behavioral Sciences Program 83

Dental Research Institutes and Centers Program 93

PART IV - INTRAMURAL RESEARCH

PART V - CONTRACTS

REPORT OF THE EXTRAMURAL PROGRAMS

NATIONAL INSTITUTE OF DENTAL RESEARCH

July 1, 1973 - June 30, 1974

by

Dr. Clair L. Gardner
Associate Director for Extramural Programs

The Extramural Programs of the National Institute of Dental Research make up one of the three organizational components of the Institute directly concerned with research. The 15 scientist administrators who lead NIDR's Extramural Programs serve as the principle administrative arm through which the Institute maintains its position as the chief architect of dental research in the United States. Under this arrangement Institute staff participate in the planning, development, funding, and evaluation of research programs ranging from those that deal with basic underlying causes of oral diseases to those that evaluate practical public health measures for disease prevention. These programs include both laboratory and clinical endeavors involving a wide spectrum of scientific disciplines.

To foster a high level of continuing research accomplishment on a broad, comprehensive scale, the Extramural Programs make awards of varied types and sizes. These awards include institutes or centers grants, regular grants, small dental research awards and contracts. For the training of future researchers, support is provided to promising young scientists by means of training grants, post-doctoral fellowship grants of several types, and career development awards. In setting the stage for fruitful scientific and academic achievement, Extramural staff have made extensive efforts to stimulate an atmosphere of enthusiasm about oral biology research. They have sought to do this in universities, in hospitals, in research institutes, and in industry, for purposes of developing a maximal research effort throughout the nation and the world. The evidence at hand indicates that the increasing number of scientists now working on dental problems is indeed accelerating the development of knowledge which may soon permit the prevention and control of certain oral diseases.

Following last year's adaptation to internal reorganization, the Extramural Programs of NIDR this year achieved a solidification of staff effort as they moved towards program goals. The three new special assistants to the Associate Director meshed their efforts successfully with those of program leaders so that the research being carried out under individual

project grants, and that being done in program projects, have been closely interwoven with each other and with the broader research efforts being carried out in the Dental Research Institutes and Centers; and training activities, as complicated as they have been, have at least been appropriately aligned with ongoing research projects and in accord with reasonable manpower objectives. While each program area appears to have sharpened its focus and consistently moved toward its own goals, in every instance, the staff of the program has always remained aware of how the program is related to and is complementary to other institute programs and to the overall mission of the NIDR. Emphasis during the year has thus been on consolidation of effort, more efficient use of both staff, and of research dollars, improvements in the development and management of new projects and, in general, a quickened pace of administrative and scientific accomplishment.

The designation last year of three special assistants in the Extramural Programs appears to have been a worthwhile move which has indeed led to the intended goal of greater communication and heightened awareness among staff members about the activities of every program. Some of the specific contributions of these special assistants are outlined in the text to follow.

The Special Assistant for Program Coordination served as editor of the Extramural Program Annual Reports, as executive secretary of the Periodontal Diseases Advisory Committee, and as a member of the National Caries Program Executive Committee. He also participated in the planning and execution of certain workshops, organized and moderated the NIDR-IADR Forum, and prepared written material for various extramural purposes, such as the FY 76 Research Fellowship Budget Justification. As a staff worker in the Periodontal and Soft Tissue Diseases Program, he coordinated one workshop and moderated part of another, developed two research contracts, authored the program annual reports for FY 1973 and FY 1974, and performed other scientist administrator duties as needed.

The Special Assistant for Research Manpower prepared the phase-out plan for the old training program and monitored these programs by making site visits. For the Weinberger fellowship program he aided in the formulation of the special NIDR supplemental guidelines, drafted reports and analyses relating to past, present and future training activities, and served as executive secretary of the Ad Hoc Review Committee which evaluated the old training grant applications and the new Weinberger institutional awards. As a staff worker in the Periodontal and Soft Tissue Diseases Program, he organized a scientific workshop, developed contract proposals, and performed other program duties. Currently he is engaged in developing plans to encourage applications from young scientists, as described in a later section of this report.

Although the activities of the Special Assistant for the Dental Research Institutes and Centers (DRIC) are reflected in the individual report of that program, it should be mentioned specifically that he serves as

executive secretary of the DRIC Advisory Committee, which periodically reviews the research of each institute or center in the manner of a study section. In addition, he has served as executive secretary and principal staff resource person on the committee to evaluate the overall DRIC program, and has participated in special projects such as the Manpower Utilization Study and the preparation of the FY 76 Fellowship Budget Justification.

There were few personnel changes throughout most of Fiscal Year 1974, but towards the latter part of the year, a significant number of departures and replacements of professional individuals took place. Following the retirement of Dr. Louis J. Pecora and Dr. Louis W. Wachtel from service in the Restorative Materials Program, Dr. Thomas Valega, of the Periodontal and Soft Tissue Diseases Program was appointed Chief of the Restorative Program. In addition to Dr. Valega, Dr. John Goggins and Dr. Richard L. Hayes have also relinquished their duties in the Periodontal Program, Dr. Hayes having transferred earlier in the year to join the Pain Control and Behavioral Studies Program and to participate in special training program endeavors, and Dr. Goggins having left to assume the important post of Associate Director for Collaborative Research. Dr. Samuel Kakehashi, who served part of the year in the Restorative Materials Program, has been appointed the new Chief of the Periodontal and Soft Tissue Disease Program, with the position recently vacated by Dr. Valega ramining to be filled. In addition to these changes involving professional staff, five key supporting staff members are being recruited to fill essential vacancies. We are also extremely pleased that two visiting scientists will join the staff of the Extramural Programs for the coming year. Colonel Robert Johnson, of the United States Army's Dental Research Unit, will be on duty in the Pain Control and Behavioral Science Program, and Dr. Carla E. Evans, a National Cancer Institute scientist who recently completed research training at Harvard Dental School (an NIDR supported Program) will supplement the staff of the Craniofacial Anomalies Program.

STAFF ACTIVITIES

Throughout the year, NIDR Extramural Programs staff maintained constant communication with members of the scientific community to stimulate development of new research programs and to keep investigators promptly informed of changes in government policy, particularly on matters of research training. This level of communication was achieved through a combination of written correspondence, telephone discussions, direct personal contact, and participation in scientific meetings and workshops. During the past year, program staff made approximately 70 visits to institutions to program and monitor proposals in research and research training. They made site visits for evaluative purposes in more than 40 instances, and they participated in more than thirty different scientific meetings. In addition, five different professional development meetings and courses were attended by one or more of the Extramural staff. In accord with plans described in last year's annual report,

Extramural staff have this year emphasized planning and evaluation and the monitoring of ongoing research grants and training grants. To aid in achieving optimal program planning, informal accountability sessions were held within Extramural staff to review in depth the extent to which each of the programs was on schedule in advancing toward its goals. For monitoring purposes, special efforts were made to plan travel so that the status of all old training grants could be reviewed on site and all research grants over $100,000 in magnitude could also be directly assessed. In one program all research grants over $50,000 were examined and discussed on location.

Continuous contact with the scientific community is considered critical to the development and funding of quality research projects. Thus, staff does not rely entirely on specific visits to research locations, but also sees to it that there is a good deal of other interaction with investigators. For example, this past year a special effort was made to set the stage for as much communication as possible with applicants or potential applicants at the meetings of the American Association of Dental Schools and the International Association for Dental Research (IADR) in Atlanta. Prior to these meetings staff mailed out information indicating that the NIDR would maintain a consultation suite throughout these meetings, and would also hold an open forum during the IADR meeting to discuss research grants, contracts, and training and fellowship programs. The forum consisted of brief staff presentations outlining recent changes in policy and describing research areas of current emphasis in each program, as well as open discussion. The forum appeared to be well received as a worthwhile endeavor by most of the two hundred or so individuals who attended the session. For the 1975 meeting of the American Association for Dental Research (AADR), the largest division of the IADR, Institute staff will again conduct a similar forum. Through special arrangements, NIDR will also support travel for American scientists participating in the IADR meeting to be held in London in 1975. In order to make funds available for this purpose, extramural staff initiated the development of a block grant to the AADR to ensure transportation for a significant number of worthy investigators.

NIDR support of the IADR, Dentistry's principal research organization, has been a major factor in the development of this scientific organization. In a few decades the annual meetings of this association have grown from small gatherings of scientists discussing a few papers to major meetings involving more than 4,000 scientists and more than 900 presentations. By providing support for the meetings of the IADR, its publications, its fellowship programs and the research of its members, NIDR has helped to elevate the scientific stature of this organization and to enhance its effectiveness.

Committees and Special Projects

The development of the Annual Reports for the NIDR Extramural Programs represents a project of considerable magnitude involving the efforts of

individuals from all the programs. Last year an attempt was made to improve these reports so that they would be more comprehensive and more uniform. It was felt that such documents, if carefully prepared, could serve as resource material to aid staff in fulfilling the many requests for written material which arise throughout the year. To achieve reports with the desirable characteristics, one of the Special Assistants, Dr. Rizzo, was assigned the responsibility for developing the final reports. Since this arrangement seemed effective last year in producing a report of suitable quality, the same approach has been followed this year. After nearly three months of intense drafting, rewriting and revising activities on the part of various program staff and the editor, the reports were completed and assembled. It may be noted that this year's combined reports are approximately 50% longer than last year's. This increase is believed to reflect both an increase in staff activity, and a more comprehensive reporting job.

Until recently, the Extramural Programs have supported little contract research except for that maintained by the Restorative Materials Program. To facilitate the expansion of contract activities in all of the Extramural programs, a contract review committee was established early in the year. This committee, now headed by Dr. Kenneth Hisaoka has responsibility for monitoring the progress of all of the contracts initiated in the Extramural Programs and also for reviewing the requests to initiate new contracts. According to the committee's records, FY 74 saw the negotiation of six new contracts in four Extramural program areas. Two of the new contracts, awarded by the Periodontal and Soft Tissue Diseases Program, will attempt to identify chemical agents for plaque prevention; two others, developed by the Mineralization, Salivary Secretions, and Nutrition Program will study the effect of calorie and protein deficiency on the integrity of the oral mucosa in primates; and the two remaining contracts, initiated by the Restorative Materials Program, will seek to develop improved materials for maxillofacial prostheses. In addition, more than a dozen protocols for contract projects are under preparation at the present time, and most of these are expected to be negotiated during the coming fiscal year. It is anticipated that the current progress towards the development of contract programs will supplement ongoing efforts being supported by grants and will add greatly needed flexibility to the overall Extramural Programs.

Another endeavor of significance was the development of the Operations Manual for Scientist Administrators, a reference book designed to help scientist administrators fulfill their responsibilities in the Extramural Programs of the National Institute of Dental Research. The first edition of this monograph was compiled under the direction of Mr. Nelson E. Lyttle, who served as a consultant for the project. Since this guidebook includes precisely delineated job descriptions for scientist administrators at various levels, as well as managerial procedures necessary for the multiple functions performed by staff, it should enable the staff to better understand the entire complex of Extramural operations and to perceive more clearly their own roles and capabilities. The impressive assemblage of useful material in the manual includes chapters on pertinent legislation,

on the organization and mission of the Institute, on referral guidelines for grant applications, on the review of grants and contracts, and on the proper treatment of human experimental subjects, as well as notes on program evaluation and on the development of improved scientific conferences.

Another group concerned with administrative practices was the Administrative Affairs Committee, which recently updated the telephone systems within NIDR-EP, and has coordinated the acquisition of badly needed dictating equipment and memory typewriters. This committee also plans to work out procedures to speed up the flow of administrative documents within the Institute.

An important project carried out by Extramural Program staff during FY 74 was a manpower utilization study to evaluate the manpower requirements of the Extramural Programs so that reasonable forecasts for the future could be made. Dr. Kenneth Lynn, Dr. William E. Rogers, Jr., and six members of the Extramural Program staff contributed more than 60 man-days of professional work in this endeavor. This study represents an implementation of the HEW policy on manpower management emanating from a House Appropriations Committee directive of 1970. As a result, the NIDR staff committee, with the aid of an HEW-appointed consultant has attempted to design a system for analyzing administrative duties and estimating the work load, so that productivity indices could be derived. During the year, the committee developed data forms and conducted several surveys to compile pertinent information in a suitable display. A comprehensive report is currently in preparation. It is anticipated that the system finally adopted will facilitate the immediate analysis of manpower work loads and allow prompt forecasts of future needs.

Another important committee was given the charge of conducting a thorough evaluation of the Dental Study Section to determine whether any recommendations should be made to the Division of Research Grants regarding this initial scientific review group. This committee, composed of eight NIDR staff, met five times during the year to discuss whether the Dental Study Section might be modified, or else dissolved and replaced by a study section of a different character and purpose. In one meeting of this committee, two staff members of the Division of Research Grants contributed their views on the subject. The committee is currently preparing a report which will make suggestions on such aspects as the name of the study section, referral guidelines, priority scores, potential reorganization, composition and responsibilities of the study section.

The purpose of another special project involving the Extramural Programs is to develop an evaluation method for measuring the success of the Dental Research Institutes and Centers. It is intended that this project, begun in FY 73, will eventually produce a comprehensive assessment of the total impact of the Institutes and Centers Program. The study will determine how well the Institutes and Centers have followed their guidelines, achieved their original objectives, and served as an effective means of accomplishing research. During FY 74, staff and consultants made progress in developing a detailed evaluation outline to be used in the actual evaluation project which will be initiated in FY 75.

Another recently formed staff committee has the purpose of organizing a multi-pronged programming approach to stimulate the involvement of young scientists in oral research problems. This committee is currently at work developing methods and materials to encourage the submission of applications for fellowships and for the small grants called Special Dental Awards (R-23). To identify new applicants the committee plans to search the files of the General Medical Sciences Institute of NIH and to consult with established scientists. To inform potential applicants and other interested persons, the staff plans to contact individuals by telephone, letter or visit, to distribute by mail specially prepared information kits, and to publish broad announcements in scientific journals. The staff believes that a concentrated programming effort of this type may exert a long-range impact on the maturation of oral research.

Workshops and Meetings Sponsored

In addition to their participation in a large number of scientific meetings developed by other organizations, NIDR Extramural staff invested a large portion of their professional effort in the development of 11 scientific workshops, 5 international meetings, and 3 advisory committee meetings. Scientists from all parts of the world, expert in a variety of fields, participated in these workshops to make their latest information and advice available to staff for planning purposes. The emphasis on activities of this nature is fully consistent with HEW concern for evaluation and the provision of 1% set aside funds for such purposes. In an attempt to achieve these comprehensive evaluations of research progress, staff made full use of these funds. Staff and their consultants in these endeavors are now busily engaged in summarizing the final reports of these fruitful meetings. The proceedings of most of the workshops will be published in the near future.

The Periodontal and Soft Tissue Diseases Program conducted 4 of the 11 workshops. One was concerned with the biochemistry of connective tissue with a view towards explaining how inflammatory processes can cause loss of structural elements in periodontal disease. Another workshop consisted of highly detailed discussions of direct mechanisms by which immune processes may cause periodontal tissue degradation. In a third workshop developed by this program, discussions were held on the morphology, the chemistry, the microbiology, and pathogenicity of dental plaque associated with both caries and periodontal diseases, and on the use of animal models in studying these diseases. A fourth meeting of this program assessed the state of knowledge concerning aphthous ulcers and recommended several approaches for expanding research in this important but neglected field. In addition, staff of this program sponsored three seminars and one international symposium. The three meetings of the Periodontal Diseases Advisory Committee held during the year included discussions on varied aspects of research on the etiology of these diseases, and on specific research related to the inhibition of dental plaque. The Committee also considered potential staff approaches to planning for the development of new research manpower, and discussed the advantages and disadvantages of establishing research centers for the study of periodontal disease.

The Craniofacial Anomalies Program held four workshops and provided partial support for two scientific meetings. In one workshop participants discussed neurosurgical and postoperative problems arising from craniofacial surgical habilitation procedures. And in another workshop, specific oral and plastic surgery problems were considered. In a third meeting, an in-depth assessment of research on the utilization of orthopedic procedures in the correction of craniofacial malformations was made. The remaining meeting conducted by this program had the more general purpose of persuading developmental biologists to become involved in research on craniofacial malformations. In addition, the program sponsored a meeting on mandibular function and partially supported a large international conference on cleft lip/palate. The Restorative Materials Program again partially supported the Clemson University International Symposium on Biomaterials, an annual conference on reconstructive materials and implantation. The Program also conducted a large symposium in conjunction with a small advisory panel meeting with the purpose of producing advice for the staff on future program development in this area. The proceedings of this 3-day symposium/conference have been published and distributed. The Mineralization, Salivary Secretions Program convened two ad hoc advisory committee meetings, one on mineralization research and one on nutrition research. The first committee recommended that research on the chemistry of calcium phosphate be reduced and the other committee recommended an overall expansion of efforts in the nutrition field. Finally, the Pain Control and Behavioral Studies Program provided key financial and consultative support to enable the Section on Dentistry of the American Association for the Advancement of Science to hold a Symposium-Workshop on "The Control of Pain" at its annual meeting in San Francisco in February 1974.

A complete list of Extramural Workshops and Meetings during FY 74 is given below:

STAFF INITIATED WORKSHOPS

1. Mechanisms of Connective Tissue Degradation
2. Immunological Mechanisms in Periodontal Disease
3. The Pathogenicity of Dento-bacterial Plaque
4. Problems and Perspectives of Recurrent Aphthous Stomatitis
5. Neurosurgical Problems in Craniofacial Habilitation
6. Surgical Research Problems in Craniofacial Habilitation
7. Research on Craniofacial Orthopedics
8. Developmental Biology and Craniofacial Anomalies
9. Symposium/Conference on Dental Biomaterials Research Priorities

10. Mineralization Research Workshop

11. Nutrition Research Workshop

12. Periodontal Diseases Advisory Committee (3 regular meetings)

NIDR SUPPORTED MEETINGS

1. International Symposium on the Immunoglobulin A System
   University of Alabama

2. The Second International Congress on Cleft Palate
   Copenhagen

3. Research on Mandibular Function and Dysfunction
   Buffalo

4. The Sixth Annual International Biomaterials Symposium
   Clemson University

5. AAAS Symposium/Workshop on the Control of Pain
   San Francisco

For the future, NIDR Extramural staff are concluding plans to hold seven workshops in the following areas: Clinical Oral-Facial Pain Syndromes, Techniques for Measuring Anxiety Related to Dentistry, Description and Nomenclature of Craniofacial Anomalies, Psycho-Social Aspects of Craniofacial Malformations, Orthognathic Surgery, Malnutrition in Dental Disease, and Clinical Applications of Salivary Gland Research. In addition, joint cooperation between intramural and extramural staff has resulted in the scheduling of an NIDR-sponsored scientific symposium on "Mediators of Tissue Destruction in Relation to Periodontal Disease" for the 1975 meeting of the American Association for Dental Research in New York.

Research Funding

During FY 74, NIDR research funding for all types of research grants reached a total of nearly $25 million for 277 grants. As shown in Table 1, this included the grants supported by the National Caries Program and grants to the large university-based Dental Institutes and Centers, as well as those funded by the categorical extramural programs. Table 1 also classifies funding by type of grant and, in addition, differentiates between awards made from FY 74 appropriations and those made from funds impounded in FY 73 and released in FY 74. Among the research grants supported by the NIDR Extramural Programs from FY 74 appropriations were 141 noncompeting continuation grants, 19 competing renewal grants, 48 new grants, and 14 supplemental awards. From funds impounded in FY 73 and released in FY 74, the Extramural Programs were able to fund 2 competing renewal grants, 11 new grants, and 2 supplemental awards. Among

FY 74 Awards were 58 small grants (R23) for young investigators. It was encouraging to note that only 55% of the funds expended were awarded for noncompeting continuation grants, leaving 45% uncommitted and thus available for new grants or new phases of continuing projects (competing renewals). While the total number of grants supported by all programs in FY 74 (277) was very close to that of FY 73 (281), the number of new grants initiated this past year was almost double that of the previous year. This was due in part to the release of impounded funds. Table 2 shows how FY 74 research grant funding was distributed among the individual categorical programs and the Dental Research Institutes and Centers. Approximately half of these funds were consumed by two programs: the Periodontal and Soft Tissue Diseases Program and the Craniofacial Anomalies Program. In the Periodontal Diseases Program which funded 28 new grants there was a significant increase in studies of inflammation, and new projects were initiated on Herpes virus infection, cancer, and aphthous ulcerations. Eighty-five percent of the funds of this program continue to be devoted specifically to periodontal disease. The Craniofacial Anomalies Program spent the largest portion of its funds for cleft lip and cleft palate research, with one-third of its resources being devoted to this area. Nevertheless, basic studies pertinent to all types of craniofacial malformations continued to command substantial support from this program. The Restorative Materials Program emphasized adhesives, implants, and maxillofacial prosthesis materials in its initiation of new grants and contracts this past year. The program on Mineralization, Salivary Secretions and Nutrition managed to reduce its support of grant projects dealing with inorganic calcium phosphates as recommended by an ad hoc committee. This Program funded 3 new grants on salivary secretions and initiated 2 grants on nutrition. Programming efforts by staff of the Pain Control and Behavioral Studies Program have resulted in the initiation of a new grant to study acupuncture in relation to dental pain, one of the few projects of this type funded so far by NIH.

Table 1. NIDR RESEARCH GRANT FUNDING DURING FY 1974*

A. From FY 1974 Funds

	Non-Competing		Competing		New		Supplemental		Totals	
	No.	$(000s)	No.	$(000s)	No.	$(000s)	No.	$(000s)	No.	$(000s)
CP*	27	$1,949	6	$507	13	$736	-	-	46	$3,192
EP*	141	7,575	19	2,029	48	2,011	14**	$339	208	11,954
TOTALS	168	$9,524	25	$2,536	61	$2,747	14	$339	254	$15,146

B. From Funds Impounded in FY 73

	Non-Competing		Competing		New		Supplemental		Totals	
	No.	$(000s)	No.	$(000s)	No.	$(000s)	No.	$(000s)	No.	$(000s)
CP*	-	-	1	$492	4	$232	-	-	5	$724
EP*	-	-	2	61	11	1,044	2	430	13	1,535
TOTALS	-	-	3	$553	15	$1,276	2	$430	18	$2,259
CP* TOTALS	27	$1,949	7	$999	17	$968	-	-	51	$3,916
EP* TOTALS	141	$7,575	21	$2,090	59	$3,055	16	$769	221	$13,489
DRIC* TOTALS	5	$7,150	-	-	-	-	-	-	5	$7,150
GRAND TOTALS	173	$16,674	28	$3,089	76	$4,023	16	$769	277	$24,555

* Includes Regular Grants, Special Dental Research Awards, Program Projects, and Clinical Center Grants.
EP* Extramural Programs.
CP* Caries Grants Branch of National Caries Program.
DRIC* Dental Research Institutes and Centers.
** Figures in this column not included in totals.

Table 2. RESEARCH GRANT FUNDING BY NIDR EXTRAMURAL PROGRAMS DURING FY 74*

Program	No. Grants	Amount $(000s)
(2) Periodontal and Soft Tissue Diseases	82	$4,690
(3) Craniofacial Anomalies	61	5,101
(4) Restorative Materials	32	1,236
(5) Mineralization, Salivary Secretions and Nutrition	37	2,114
(6) Pain Control and Behavioral Studies	9	404
(7) Dental Research Institutes and Centers	5	7,150
	226	$20,695

* Includes grants awarded with funds impounded in FY 73 and released in FY 74. Does not include grants by the National Caries Program.

Training

The picture of research training programs at the NIH during FY 74 was marked by continuing confusion which involved the impoundment of funds, the initiation of the phase-out of the old training program, a dramatic court judgment, the resurrection of the old training program, and the simultaneous initiation of a new program. Early in FY 74, NIDR staff were proceeding with the approved phase-out plan described in last year's annual report. During the course of the year, however, the court decision was made directing that HEW release the funds impounded in FY 73 so that all applicants previously eligible for FY 73 training awards would be funded as originally intended. The court order also directed that the processing of all applications pending at the time of the impoundment should be completed, and awards made to those found acceptable for funding. These actions reinstated the old training grants for a time. Meanwhile, a formal announcement was made in December 1973 of the inception of the new Weinberger postdoctoral program by which funds were designated for the support of Individual Fellowship and Institutional Fellowship grants. This postdoctoral fellowship program was intended to emphasize the support of individuals rather than the support of institutional departments, and was specifically designed to develop investigators for areas of biological science where there is a known shortage of manpower. To inform potential applicants of the research areas in which future manpower would be needed, NIDR staff prepared a special supplement to the "NIH Guide to Research Manpower Programs," and distributed this document widely throughout the scientific community soon after the

announcement, so that the extremely short deadline for submission could be met. The establishment of this second program meant that the NIH now would have two training programs running simultaneously. However, the immediate impact of the court order and the announcement of the new program was that plans had to be made to rapidly review applications for both the old and the new training programs, so that those to be funded could be processed before the end of the fiscal year. The review of NIDR applications was accomplished by convening a special ad hoc review group to evaluate the competing renewal applications from the old training program and the new applications for the new Institutional Fellowship Grants. Dr. Robert Schuellein, Special Assistant for Manpower, organized this ad hoc committee and served as executive secretary. Meanwhile, the Division of Research Grants arranged to review the Individual Postdoctoral Fellowship Applications. It was also necessary to hold a special meeting of the National Advisory Dental Research Council in April to complete the formal review of these applications sufficiently early to permit final processing and funding in FY 74.

Table 3 describes the pattern of NIDR funding of training and fellowships during the five-year period from FY 72 projected to FY 76. From the three upper bands of this table, it can be seen that all of the training grants and other components of the old program are expected to continue their rapid decline. As the table indicates, however, this program will not be completely phased out until after FY 76. The Career Awards and Career Development Awards are expected to continue at some level of activity, even though figures for these awards are not shown in that last three columns. The reason for this omission is that these awards are no longer paid from training and fellowship appropriations, but instead are now paid with funds allotted for research. The lower two bands show that the Weinberger Postdoctoral Fellowships Program has made a substantial beginning with awards made already to support nearly 100 postdoctoral fellows. To fulfill the anticipated needs of the Institute's programs, it is expected that the number of these awards will increase in the future. For example, in FY 76, it is projected that support will be furnished for approximately 600 postdoctoral candidates at an expenditure of $9 million.

Table 4 describes NIDR research training support of both the old and the new programs with funds derived from FY 74 appropriations and from FY 73 released funds. NIDR Extramural Programs supported 60 "old-type" training grants which provided training for 298 trainees and supported 18 fellows for the total sum of $4.4 million. The Institute also initiated the new Weinberger fellowship program by making awards for 15 Institutional grants to support 52 postdoctoral fellows at a cost of $883,000, and expended $526,000 to support 47 individual fellows. The total outlay of training funds for the year was close to $6 million. Sixty percent of these funds was divided equally between the Periodontal and Soft Tissue Diseases Program and the Craniofacial Anomalies Program for the training of 256 scientists in basic science disciplines related to growth and development, and in the fields dealing with the biology of disease processes.

Table 3. FIVE YEAR DISTRIBUTION OF NIDR TRAINING AND FELLOWSHIP FUNDS

Funding Mechanism	FY 72	FY 73	FY 74*	FY 75+	FY 76+
No. Training Grants (OLD)	90	87	60	48	34
No. Trainees	435	380	298	225	160
Funds$(000s)	$5,698	$2,989	$4,189	$3,331	$2,276
No. Postdoctoral Fellowships (OLD)	30	16	8	2	2
Funds $(000s)	$285	$158	$75	$19	$21
No. Special Fellowships (OLD)	31	22	10	2	0
Funds $(000s)	$487	$349	$144	$35	0
No. Career Develop. and Career Awards (OLD)	26	22	17	-	-
Funds $(000s)	$582	$506	-**	-	-
No. Institutional Fellowship Grants (Weinberger)	-	-	15	17	53
No. Fellows	-	-	52	77	183
Funds $(000s)	-	-	$883	$1,396	$3,016
No. Postdoctoral Fellowships (Weinberger)	-	-	47	115	281
Funds $(000s)	-	-	$526	$1,504	$3,877
Total No. Individuals	522	440	432	421	633
Total Funds $(000s)	$7,052	$4,002	$5,822	$6,285	$9,180

*Figures in this column include funds impounded in FY 73 and released in FY 74
**Paid from research funds after FY 73.
+Figures in this column are estimates.

TABLE 4. SUMMARY OF NIDR RESEARCH TRAINING, AND FELLOWSHIP BUDGET

FY 1974

(Amounts given in thousands of dollars)

	Old Training Program							New Research Fellowship Program					
			FELLOWSHIPS				Total	T22 (Institutional)			F22 (Individual)		
	Grants	Trainees	Postdocs.	Amt.	Specials	Amt.	Amt.	Grants	Fellows	Amt.	Fellows	Amt.	Total Amt.
Caries Program	1	2	0	--	0	--	194	0	0	--	3	34	34
Periodontal Diseases Program	19[1/]	87	5	50	4	60	1,367	6	20	323	18	205	528
Craniofacial Anomalies Program	16[2/]	76	1	8	4	69	1,016	7	26	455	15	161	616
Restorative Materials Program	8	34	0	--	0	--	555	0	0	--	2	21	21
Mineralization, Salivary Secretions, and Nutrition Program	7	34	0	--	2	20	484	1	2	33	8	95	128
Pain Control and Behavioral Studies Program	9	65	2	17	0	--	808	1	4	72	1	10	82
TOTALS	60	298	8	$ 75	10	$ 149	$ 4,434	15	52	$ 883	47	$ 526	$ 1,409

1/ Includes 2 dual degree programs.
2/ Includes 1 dual degree program.

RESEARCH HIGHLIGHTS

Research findings of NIDR-supported investigators are described in the program reports to follow. In this section, selected findings of special interest are presented in a condensed form. Among the research highlights were additional findings to support the contention that there may be bacterial specificity in the etiology of periodontal disease. Studies of the destructive condition called periodontosis have implicated a group of Gram-negative organisms as possible causative agents in this severe periodontal disease. These organisms are suspected because they were isolated from the sites of disease activity, they produced periodontal bone loss in gnotobiotic animals, and their elimination from diseased pockets arrested the disease. Studies on bone resorption have shown that the production of the bone resorption factor in cell-mediated immune inflammation requires two types of cells, and that humoral immunity mechanisms can also cause local bone resorption. It was found that lysosomal enzymes were not overtly destructive to epithelial cells but did cause the cells to be disrupted from their attachment surface, a finding which may explain why gingival epithelial cells become separated from each other in gingivitis. Studies of chronic inflammatory disease revealed that sensitized lymphoid cells release substances harmful to fibroblasts, the cells which produce collagen fibers and other structural tissue elements. In complementary studies, it was shown that activated lymphocytes also produced substances which turn on macrophages, and cause these phagocytic cells to release biochemical substances causing connective tissue degradation. Because of the occurrence of serum antibody to organisms from periodontal plaque and the presence of immunoglobulins in gingival tissues, it is believed that antigen-antibody complexes play a role in disease. New support for this concept came from studies showing that specific immunoglobulin and complement components were present in inflamed gingiva. In research on the prevention of periodontal disease, the efficacy of antimicrobial agents in preventing plaque was tested. Kanamycin alone protected handicapped children from gingivitis for nearly a year. Three daily applications every 5 weeks proved effective for 40 weeks. Actinobolin, an antibiotic with properties favorable for oral use, was shown to inhibit periodontal disease in rice rats. Studies showing that aspirin inhibits prostaglandin synthesis and bone resorption have led to the speculation that aspirin might be useful in the management of periodontal disease. Since aspirin in the blood of arthritis patients reaches levels that can inhibit bone resorption, some researchers recommend that clinical studies of the aspirin effect be conducted immediately. In vitro experiments indicated that salivary glycoproteins may protect the soft tissues of the oral cavity against bacterial infection by means of specific chemical components. The salivary glycoproteins prevent the adherence of bacteria, because the glycoproteins have specific binding sites just like those on the epithelial cells. Thus, the bacteria stick to the glycoprotein binding sites instead of adhering to and infecting the epithelial cells.

In research on growth and development, evidence was obtained that information may be transferred between the epithelial and mesenchymal layers of a developing tooth via the RNA-containing matrix vesicles. Further support

for intercellular communication has been obtained through studies in which separate samples of tooth epithelium and of mesenchyme were combined in tissue culture to produce teeth with predetermined structural characteristics. In a new development in cleft lip and palate research the process of secondary palate formation was observed in exteriorized mouse embryos still attached to the maternal organism. The technic permitted direct observations of the effects of teratogenic drugs on palatal closure and on tongue displacement. Recent results suggest that cortisone produces cleft palate by reducing neuromuscular activity, thus preventing the normal displacement of the tongue from between the palatal processes. In epidemiologic studies of genetic components in the causation of cleft lip and palate it was found that a major dominant gene may be important, since every Haliwa Indian with a cleft was related to one woman born in 1832. New experimental data indicated that simulated palatal surgery on normal animals drastically reduces skeletal growth on the operated side as compared to the unoperated side. A promising group of experiments on mechanisms of bony suture formation has opened up the possibility of developing a new biological habilitation measure. The procedure envisioned involves the transplantation of viable bony sutures into areas where sutures are missing (cleft palate), or into areas where sutures have prematurely closed (Apert's Syndrome). Attempts to define the stimuli involved in bone formation and resorption suggest that cyclic AMP may mediate a signal in mechanically stressed bone. These results may have implications in orthodontic treatment. In another study related to orthodontics it was concluded that the best estimate of a patient's facial growth potential may be determined by examining relatives in the immediate family rather than by relying on population norms. It was found in another clinical study that the orthodontic activator device was most effective in treating malocclusions during the transitional dentition. Apparently, the activator repositions the mandible without inducing an increase in mandibular length.

Collagen studies have indicated that the distribution of crosslinks in dentin collagen is different from that of skin. Other studies demonstrated the importance of nutrition in the formation, secretion and maturation of collagen fibers. For example, oxygen, iron and ascorbic acid were shown to be cofactors in the hydroxylation process which is necessary for the collagen to maintain normal structure, and Vitamin D was shown to be important for the development of crosslinks during the normal maturation of bone collagen. In a study of highly localized portions of human enamel, it was found that the solubility of the mineral varied according to individual, according to the tooth, and according to the exact location on the tooth. These findings may explain the variation in caries susceptibility observed in different teeth and in different parts of teeth. In a promising animal study with clinical overtones, it was shown that demineralized allogeneic bone matrix implants induced the regrowth of the condylar portion of the temporomandibular joint. In studies on salivary secretions, two new groups of proteins were discovered. The properties of one suggest that they may play a role in the formation of the early pellicle which leads to bacterial plaque development. Since the other group has properties similar to proteins of phagocytic cells, it is believed that these proteins may possess antibacterial properties.

In nutritional studies of the past year, scientists confirmed earlier studies indicating that protein deficiency maintained only during gestation and lactation not only caused growth stunting but also increased susceptibility to dental caries in later life. The investigators believe that the caries susceptibility in these studies may be related to the saliva, since they also found that the malnourished animals produced saliva which was several times less in volume and in protein concentration than the saliva of control animals. In metabolic studies in humans, it was shown that calcium retention was increased by the presence of phosphate in the diet. Meanwhile, animal studies generated further evidence that fluoride may be an essential dietary element during the early growth period. These studies suggest that fluoride may be required for optimum utilization of dietary iron.

A study on pain relief in ambulatory patients showed that Fentanyl is preferable to the more commonly used meperidine (Demerol). Although the analgesic effect of Fentanyl was only equal to that of meperidine, recovery from sedation was quicker with Fentanyl and there was less of a depressant effect on respiration and blood pressure with Fentanyl than with meperidine.

Prepared by A. A. Rizzo

ANNUAL REPORT FY 74

PERIODONTAL AND SOFT TISSUE DISEASES PROGRAM

INTRODUCTION

The Periodontal and Soft Tissue Diseases Program fosters research related to periodontal diseases, oral ulcerative diseases, oral cancer, and other soft tissue disorders, including those of the dental pulp. The ultimate mission of the program is to develop new knowledge which will lead to the prevention and eradication of these diseases throughout the world. Since the diseases named are multifactorial in etiology and complex in manifestation, the program supports research and training efforts in a wide variety of subject matter. Included are studies on bacteria and viruses, their biology, chemistry, effects on the host, and behavior in the oral environment, as well as studies on the molecular biology of the normal and abnormal metabolism of the mucosa and periodontium. Within the broad spectrum of biological studies supported, special attention is given to the specific biochemical and immunologic mechanisms involved in the pathologic processes of inflammation and tissue destruction. It is hoped that comprehensive studies of the chemical steps involved in periodontal and soft tissue disease progression will reveal optimum points at which inhibitory, preventive agents can arrest these diseases.

A significant trend which became manifest this past year in the periodontal disease research area has been the development of a number of international collaborative ventures. These cooperative efforts involve outstanding investigators based primarily in America and Europe who appear to have joined hands to conduct studies which relate the microbial and host factors in the evolution of these diseases. These studies involve cultural microbiologists, microbial physiologists, oral biologists, immunologists, immunopathologists, connective tissue biochemists, bone researchers and clinical investigators all working intensely to generate additional biological information and to incorporate each new fact into an integrated picture of the disease process. Thus, it is becoming clear that there are many microbial inciting agents which might initiate the periodontal disease process, that the varied immunopathologic manifestations of the disease at different stages are being defined, and that a plethora of immune reactions and nonimmune inflammatory reactions could account for the net loss of connective tissue and bone. During the year there were also signs of energetic research activity on Herpes Simplex virus infections and of a resumption of at least some activity on recurrent aphthous ulcer mechanisms. These studies also emphasize disease processes and mechanisms of susceptibility. By maintaining multiple lines of communication, by direct personal contact, by participating in scientific meetings, by developing timely workshops, and by coupling these activities with the funding of quality research projects, the Institute staff has played a major role in fostering and coordinating the highly productive individual and collaborative efforts that are now reaching maturity.

ADMINISTRATIVE

During the past year, the program awarded research funds of approximately $4.7 million for 5 program projects, 58 regular research grants, 18 Special Dental Research Awards, and partial support for one international symposium. Twenty-eight of the awards were made for new research projects. In addition, direct support of $150 thousand was provided for two new contracts to identify chemotherapeutic agents for dental plaque prevention. For research training, the program awarded $1.26 million for 19 training grants to provide stipends for 87 trainees, and $110,000 to support 9 postdoctoral fellows. In addition, 1 career award and 4 career development awards were made at a cost of $117,000. Funding for the new Weinberger program included $323,000 to support 20 postdoctoral fellows on 6 institutional fellowship grants and $205,000 to support 18 individual postdoctoral fellows.

Table 1 shows the distribution of research grant funds according to subject area. The periodontal diseases component of the program consumed approximately 85% of the grant funds, the same level as last year. The most significant change in the research support this year was an increase in the support of studies of the inflammatory response in periodontal disease from 14.6% to 24.5%. As the result of staff programming activities, the research funding in the important area of Herpes virus infections increased from 0.6% to 1.1% and funding for studies in tumors of the oral mucosa increased from 5.2% to 8.0%. However, in the area of recurrent aphthous ulcers, grant funds decreased slightly, from 1.8% to 0.8%.

TABLE 1

I. Periodontal Disease	
A. Etiology	
Plaque (ecology, chemistry and metabolism, adhesion, toxic activity, salivary and dietary factors . . .	$1,134,307.
Miscellaneous factors	180,381.
B. Pathogenesis and Pathology	
Inflammatory response (Chemotactic factors, vascular effects, immune response)	1,174,824.
Tissue destruction and healing (epithelial integrity, connective tissue and bone metabolism, effect of inflammation)	1,459,782.
Miscellaneous	--
C. Diagnosis and Treatment	52,886.
D. Prevention	52,082.
Subtotal:	$4,054,262.
II. Herpes Simplex Virus Infection	51,154.
III. Recurrent Aphthous Ulcers and Similar Disorders	36,876.
IV. Tumors of Oral Mucosa and Connective Tissue	382,032.
V. Tumors of Salivary Glands	108,893
VI. Dental Pulp Studies	153,783.
Subtotal:	$ 732,738.
TOTAL:	$4,787,000.

STAFF ACTIVITIES

During the year, staff made visits to a large number of institutions to program, monitor, and evaluate proposals, and also to participate in meetings. Visits were made to 25 institutions in the U.S. to discuss a variety of potential studies in the fields of periodontal and oral soft tissue diseases, to 6 institutions to discuss the training of investigators for research in periodontal and soft tissue diseases and to 6 institutions where project site visit reviews for the evaluation of research and training grant proposals were being conducted. Staff also participated in the 7 scientific meetings listed below:

1 - NIDR 25th Anniversary Conference; Washington, D. C.; June 28-29, 1973; (Formal presentation given by Dr. Rizzo);

2 - Dental Biomaterials - Research Priorities, NIDR; Des Plaines, Ill.; August 7-8, 1973;

3 - International Symposium on the Immunoglobulin A System, School of Dentistry, U. of Alabama, Birmingham, Ala.; Oct. 23-25, 1973; (Formal presentation given by Dr. Rizzo);

4 - 114th Annual Session American Dental Association, Houston, Texas; Oct. 28-Nov. 1, 1973;

5 - American Association for the Advancement of Science, San Francisco, Calif.; Feb. 24-28, 1974;

6 - International Association for Dental Research, Atlanta, Ga.; March 21-24, 1974;

7 - Sixth International Biomaterials Symposium, Clemson University, Clemson, S. C.; April 20-24, 1974.

The following professional development meetings and courses were attended by one or more of the program staff:

1 - Program Mechanisms Committee Report Implementation, NIH-OD Retreat, Airlie House, Va.; July 11-13, 1973; (Dr. Goggins and Dr. Valega);

2 - Legal Basis, Grants and Contracts; Continuing Education Program; Staff Training, Extramural Programs, NIH; Oct. 8-10, 1973; (Dr. Valega);

3 - NIH Project Officers Training Course "Program Officials Guide to Contracting;"
Nov. 12-16, 1973, Hershey, Pa.; (Dr. Valega);
Feb. 11-14, 1974, Charlottesville, Va.; (Dr. Goggins).

RESEARCH HIGHLIGHTS

The research findings described in this section follow the outline presented in Table 1. As in earlier years, many of this past year's research highlights in the periodontal diseases issued forth from studies on etiology and pathogenesis. Perhaps, the most outstanding findings on the periodontal research scene have been the etiologic studies on the bacterial specificity of periodontal diseases. These studies, reported to some extent in the last year's annual report, have this past year brought more evidence in favor of the hypothesis that the different manifestations of periodontal disease may be caused by different organisms. Significant advances were also made in expanding the knowledge of the inflammatory phase of gingivitis and in relating the inflammatory process to mechanisms of tissue destruction. Findings have been made which explain further how inflammatory cells make active chemicals which induce cell killing, slow the production of new protein, and accelerate the degradation of soft connective tissues and bone. Such studies have continued to produce new knowledge at a quickened pace in the past few years. Advances in understanding the complex biological interactions involved in alveolar bone destruction of periodontal disease were made as a result of research employing a variety of techniques, including tissue culture and germfree animals, as well as classical biochemical and morphologic techniques. These studies have begun to bring forth significant information on the bacteriology, the cellular events and the biochemical substances associated with the localized alveolar bone resorption of periodontal disease. Meanwhile, research on other soft tissue diseases generated new findings on the salivary and immune aspects of human susceptibility to oral diseases caused by bacteria, viruses, and fungi.

Etiology of Periodontal Disease: Some of the findings highlighted in last year's report on etiology were drawn from the comprehensive efforts carried out at Forsyth Dental Center to identify pathogenic plaque organisms. According to the results reported then, it seemed clear that several different clinical disease entities could be distinguished from each other and that each one was associated with its own characteristic microbiota. In the past year, the evidence in favor of bacterial specificity in periodontal diseases has been further strengthened by continuing studies of the microbiology of the disease called periodontosis, or rapid destructive periodontitis of adolescence. Studies were made in these patients because it was believed that this rapid form of the disease might serve as a good model for discovering etiologic factors of importance in more common types of periodontal disease.

Using specially designed techniques and devices, highly localized, completely anaerobic samples were taken from deep periodontal pockets directly at the site of greatest disease activity in a small group of patients. Samples from healthy sites in the same patients were taken in exactly the same way and subsequently, a comprehensive identification of all organisms was completed. After these exhaustive studies, a larger group of patients were studied to concentrate on the predominant organisms discovered. The findings showed that the predominant cultivable bacteria present in the

pathologic sites were distinctly different from those of the normal sites in the same patient at the same time. The normal site contained the familiar Gram positive organisms such as: Streptococcus sanguis, S. mitis, Staphylococcus sp., Peptostreptococcus species, Actinomyces naeslundii and viscosus-like organisms, Rothia dentocariosa, P. acnes, Veillonella parvula, Fusobacterium nucleatum, B. melaninogenicus, whereas the pathological sites showed high numbers of Gram negative rods and a relative absence of Gram positive cocci and rods. In the normal sites only 25% of the flora was Gram negative. In contrast, more than 60% of the microbiota of the pathologic site was Gram negative, and more than 80% of these were Gram negative rods. These Gram negative rods were motile, anaerobic and not previously identified. Five groups were present: 1) Vibrios, 2) gliding fusiforms (different from known Fusobacteria), 3) small anaerobic rods (0.3X0.6 microns) of unknown derivation, 4) heterogenous, peritrichously flagellated, anaerobic rods which do not fit existing classifications, and finally, 5) large gliding rods. All patients demonstrated the above microorganisms in total and mean proportions of 30 to 80% in disease sites.

The morphologic aspects of periodontosis were examined by the Forsyth group in collaboration with University of Pennsylvania investigators. These studies revealed the following features: little bacterial plaque; many bacteria not tightly adherent to teeth; and a microbiota dominated by slender Gram negative rods and spirochetes. The adjacent gingival tissue contained many plasma cells but little vascular inflammation. It has also been observed clinically that this disease shows little plaque and inflammation.

Gnotobiotic studies conducted by investigators at Forsyth and Harvard support the possibility that the Gram negative rod forms may be the cause of the severe alveolar bone destruction which takes place. In these studies, scientists have examined the pathology of periodontal disease caused by monoinfecting Germfree animals with each of three of the Gram negative rods isolated from periodontosis sites in humans. While these animals showed little plaque and no root caries, massive destruction of alveolar bone associated with tremendous numbers of osteoclasts was observed. The soft tissue showed no plasma cells and little vascular inflammation.

To begin examining the immunologic aspects of periodontosis, collaborative studies between the Forsyth workers and investigators at Guys Hospital in London were arranged. In these studies, preparations of the suspect Gram negative organisms were tested for their ability to transform lymphocytes, a measure of cell mediated immunity. The lymphocytes of periodontosis patients failed to respond to the 5 suspect bacteria. These results suggest that such patients may be unable to mount a cell mediated immune response to certain organisms. Whether or not these early findings are related to the peculiar susceptibility of periodontosis patients can only be discovered by additional research. Meanwhile, these interesting findings point to the possibility that underreactivity of the immune system or anergy, as well as immunologic overreactivity may both be important in the periodontal disease process.

Pathogenesis and Pathology of Periodontal Disease.

Bone Resorption: Research projects attempting to identify potential host mechanisms in alveolar bone destruction have continued to rely heavily on tissue culture assays involving fetal rat bones, with little utilization of *in vivo* methods as yet. A recently discovered bone resorption stimulator derived from cell mediated immune reactions received continuing attention this year, and progress was made in implicating humoral immunity factors as possible mediators of localized resorption.

In studies attempting to relate the bone resorption of periodontal disease to the direct action of bacteria or bacterial products, workers at SUNY at Buffalo have examined the mechanisms of bone resorptive activity of lipopolysaccharide endotoxins and lipoteichoic acid from *Lactobacillus fermentii* in organ culture. These substances had been shown to cause osteoclastic resorption in earlier experiments. In the current studies, it was shown that the active part of both of these substances resided in the lipid portion of the molecules and not in the carbohydrate portion.

It was shown by investigators at the NIDR Intramural Program in collaboration with grantees at the University of Rochester that the bone resorption factor associated with cell mediated immunity requires cell-to-cell cooperation between macrophages and activated lymphocytes. These investigators had first shown that activated cultures of human lymphocytes produced an osteoclast activating factor (OAF) which induced bone resorption *in vitro* when the lymphocytes were stimulated with dental plaque antigens or phytohemmaglutinin. However, since the activated cultures not only contained human lymphocytes but also contained small numbers of granulocytes and macrophages, it was not clear that the OAF was produced by the lymphocytes alone. Therefore, it was necessary to purify the cells and retest them. When this was done, it was found that lymphocytes alone would not produce OAF activity, nor would cultures of only granulocytes or macrophages. However, when purified lymphocytes were incubated with macrophages at a lymphocyte-macrophage ratio of 40 to 1, the OAF activity was restored. The authors concluded that OAF production by lymphocytes requires the presence of a small percentage of macrophages. Thus, cell-to-cell interaction appears necessary for degradation of bone associated cell mediated immunity.

Related studies carried out by investigators at the University of Rochester to characterize the bone resorption factor OAF indicate that it differs from Vitamin D, prostaglandin, and from parathyroid hormone, three known stimulators of bone resorption. In these studies, it was found that OAF behaves much like parathyroid hormone on bone in culture inasmuch as it not only stimulates resorption, but it also inhibits bone formation. *In vivo* experiments, however, indicate that OAF and parathyroid hormone are not identical, because large amounts of OAF can be injected into rats without causing an elevated serum calcium or a lowered serum phosphate.

Collaborating investigators at the University of Rochester, NIDR and the University of California have obtained evidence that factors produced by humoral immunity can also bring about bone resorption in tissue culture. First the investigators confirmed earlier work showing that specific antibodies could stimulate resorption of bone in the presence of complement. Then, using rabbits deficient in the sixth component of complement (C6), they obtained evidence that the presence of complement was required. In these studies, cultures of fetal rat long bones showed prostaglandin synthesis and the resultant bone resorption when serum containing complement were added. However, when the serum deficient in the sixth component of complement was added, decreased bone resorption occurred, but the resorptive activity could be restored by adding purified C6. These results demonstrate that complement components 1-6 are required for this activity. The importance of prostaglandin in mediating this complement-dependent bone resorption was shown by two experimental findings. First, the concentration of prostaglandin was markedly increased (up to 33 fold) in the bone cultures incubated with complement as compared to those without complement; and second, when the specific prostaglandin inhibitor indomethacin was added, neither prostaglandin synthesis nor bone resorption occurred. Thus, these findings suggest a role for both complement and prostaglandin in the bone resorption of periodontal disease. The case for humoral immunity factors in localized periodontal disease is also strengthened by evidence cited elsewhere in this report that complement components fixed to diseased gingiva have been identified; and the case for prostaglandin is strengthened by the evidence already provided by University of California workers that prostaglandin is increased in periodontally diseased tissue to levels that would be expected to produce local bone resorption.
This year the same California investigators have shown that the gingival tissue itself can produce prostaglandin. This evidence was obtained by radioimmunoassay of purified lipid extracts from both human and bovine gingiva. The investigators also showed that the specific gingival synthesis of prostaglandin could be inhibited by indomethacin and by aspirin. It was of interest to find that so far, gingival prostaglandin synthetase seems to be less sensitive to inhibition by both indomethacin and aspirin than non-gingival PGE synthetase. Therefore, studies are now underway to purify the gingival preparations so that more exact testing can be done.

Other Host Mechanisms: The activity of lysosomal enzymes in the initiation and propagation of the inflammatory response is believed to involve two major mechanisms: 1) the direct release of cationic proteins and enzymes capable of degrading connective tissue; and 2) the interaction with circulating humoral factors such as complement components. In two projects this year, specific role of these enzymes in the periodontal disease process was explored. One project examined the effect of dental plaque microorganisms in causing the release of enzymes from polymorphonuclear leucocytes and the other showed that such enzymes may not only affect connective tissue components but may also alter epithelial cell function.

In the first study, carried out at the Center for Oral Health Research at the University of Pennsylvania, investigators showed that two organisms,

Actinomyces viscosus and A. naeslundii, both known to induce periodontal disease in gnotobiotic rats, caused the polymorphonuclear leucocytes to release destructive enzymes, whereas other oral organisms caused no release. Both living and dead preparations of the Actinomyces were equally effective, and their activity in causing lysosomal enzyme release was not diminished by specific antibody against the active organisms. While other evidence indicates strongly that Actinomyces may bring about disease processes through immune mechanisms, the present results suggest that these organisms may also set off disease processes by non-immune inflammatory mechanisms.

In the second study on lysosomal granules, investigators at the University of Connecticut have examined the effects of granules on monolayers of epithelial cells in tissue culture, and on histamine release. The experiments on histamine showed that leucocyte granules could cause histamine release from mast cells irrespective of the presence of absence of purified complement components. Surprisingly, the results obtained with cultured epithelium indicated that these monolayered cells remained viable even after exposure to high levels of lysosomes for 24 hours. However, a significant effect caused by the lysosomal proteins, even at low concentrations, was to disrupt the cells from their attachment surface, a phenomenon which appeared to be the result of proteolytic enzymes from granules. This finding may represent a mechanism by which leucocytes create a pathway when they migrate through epithelium in periodontal disease.

Related studies by investigators at SUNY at Buffalo and Roswell Memorial Park Institute suggest that bacterial endotoxins from periodontal plaque may also be involved in the separation of gingival cells from teeth. In these studies it was shown that a brief exposure to endotoxin preparations weakens the attachment of cultured cells to glass and to other cells. Although the mechanism of this effect was not disclosed by the research, the effect was not considered to be due to a toxic action on the cells, because the detached cells remained viable.

Ultrastructural studies of human gingiva by workers at the Center for Research in Oral Biology at the University of Washington in collaboration with researchers in Zurich indicate that fibroblast damage may constitute one of the earliest signs of periodontal disease. In a stereologic and electron microscopic study, it was shown that the sizes of fibroblasts were increased three-fold and the cells exhibited features characteristic of sick and dying cells. It was also observed that lymphoid cells were frequently seen to be intimately associated with the altered fibroblasts. These findings seemed especially significant in view of the recent discoveries that lymphoid cells release substances which damage fibroblasts.

It appeared that these findings could constitute a pictorial representation of fibroblasts being damaged by lymphocyte products. Rather than rest with this conclusion, however, it was also necessary for the investigator to examine other possible explanations. Therefore, the University of Washington scientists then designed a subsequent study to determine whether bacterial toxins could directly damage the gingival fibroblasts.

The results showed that the gingival fibroblasts avidly adsorbed the bacterial substances, but this interaction did not cause pathologic alterations, as indicated by marker enzyme assays, and by assays of the rate of collagen synthesis. These observations thus support the concept that the pathologic alterations of fibroblasts seen in human disease are probably the result of immunologic mechanisms involving lymphocytes rather than a consequence of direct bacterial toxicity.

Indeed, there is increasing evidence that one of the ways in which bacterial products set off the periodontal disease process is to first activate cells of the body's immune system, and these cells in turn stimulate a series of cellular and chemical reactions which eventuate in tissue destruction. The lymphocyte appears to be a key mediator in these reactions, as indicated already by previous references in this report to the production by lymphocytes of a bone resorption factor and of soluble substances which damage fibroblast cells. The two studies outlined next further illustrate the role of the lymphocyte in particular steps of a cell mediated immune response.

In one study by investigators at Duke University, it was shown that the interaction of lymphocytes with antigen also results in the production of a chemical substance which causes macrophages to be localized at tissue sites of immune inflammation. Macrophages are large white cells which protect the body against invasion by engulfing foreign material, including bacteria. Having already demonstrated the production of this chemotactic factor in vitro, the researchers proceeded to illustrate its formation in vivo in guinea pigs. In these experiments, it was shown that macrophages in peak numbers reached the site of immune inflammation 48 - 72 hours after the reaction began. Before this occurred, however, the inflamed site was found to contain high levels of a factor, chemotactic for the macrophages. This factor had a molecular weight of approximately 12,500 and was similar to the factor found in vitro in the earlier experiments.

In a study complementary to those just described, scientists at the University of Washington Center for Research in Oral Biology showed that bacterial antigens could cause human lymphocytes to also produce the substances which activate the macrophages once they have arrived on the inflammatory scene. When the substances from lymphocytes were incubated with cultured macrophages, the macrophages began to increase in size and activity, and to secrete increased levels of lysosomal and other cellular enzymes. Thus, while the cells themselves remained healthy and viable, they released biochemical substances capable of causing connective tissue destruction.

Complementary studies at the Dental Research Center at the University of North Carolina have produced evidence that macrophage cells consist of a heterogeneous population. This work suggests that the different populations of macrophages may have different functions. It had been shown earlier that peritoneal macrophages could be differentiated into seven distinct populations based on their separation by Ficoll density gradient. Recently it has been found that cells obtained at different density gradients not only differ in size and other morphologic characteristics but also may differ in functional characteristics. For example,

macrophages obtained in the 12% Ficoll band can phagocytize foreign substances more effectively than macrophages from other densities. On the other hand, participation in the induction of a primary immune response appears to be a function of cells in the 14% Ficoll band only. So far as some functions are concerned, all of the different macrophages appear to react the same.

Because of the widespread occurrence of serum antibodies to oral organisms and the demonstrations of the presence of immunoglobulin in human gingiva, it is believed that antigen antibody complexes play a role in human periodontal disease. New evidence supporting this concept has come from investigators at SUNY at Buffalo who have shown further evidence that both immunoglobulins and, in addition, complement components can be demonstrated in human gingival tissues. In this study, not only was it confirmed that inflammatory gingival cells contained IgG, IgM and IgA, but it was also shown that the immunoglobulin M and complement components C3 and C4 were present in inflamed gingiva in a bound form, fixed to the tissue. In a closely related study, the same group of investigators examined the chemistry of the gingival fluid of patients with severe periodontal disease to see if the pattern of protein constituents in the fluid was consistent with the immunologic findings in the gingiva described above. Serum chemistries of the same patients were examined also. While most of the protein components of gingival fluid were found to be present at slightly lower levels than in serum, there was markedly less of the C3 component of complement in gingival fluid. This finding was taken to indicate that complement was being consumed in the diseased gingiva and, as a result, the outflowing gingival fluid contained less C3. This result appeared to be consistent with the findings that C3 may become fixed to diseased gingival tissues.

In one of the few studies so far of the relationship between a periodontal disease and immune deficiencies, investigators at the Institute of Dental Research at the University of Alabama have assessed periodontal disease in individuals up to 19 years of age with isolated Immunoglobulin A (IgA) deficiency in both serum and saliva. Deficient patients showed a considerable amount of oral pathology, including severe periodontal disease, but because of a number of uncontrolled variables in the study, it was not possible to ascribe these conditions specifically to the IgA deficiency. Thus, the interpretation of this study remains equivocal. Nevertheless, the extremely severe periodontal disease seen in two of the older patients strongly indicates the need for studies which include suitable control patients for comparison.

In a cross-sectional study at the University of Texas Dental Branch in Houston the relationship between the secretion of IgA in parotid saliva and the severity of periodontal disease was examined in 78 patients. The results showed that the IgA secretion rate was significantly lower in individuals with moderate or severe periodontal disease as compared to normal subjects. Both this study and the previous one are significant in that they probably represent the earliest of many expected attempts to show a relationship between periodontal disease susceptibility and a specific immunologic factor.

Animal Models in Periodontal Research

Last year's annual report cited evidence from investigators at SUNY at Buffalo which indicated that the macaca speciosa monkey is suitable for the study of early periodontal disease. Since that report, the investigators have obtained further evidence to substantiate this viewpoint. They have shown, for example, that gingivitis can be induced in these animals by placing them on a soft diet and discontinuing oral hygiene procedures. The development of the microbial plaque and the ensuing gingivitis then procedes in a manner strikingly similar to that observed in humans. The predominant organisms cultured from diseased sites at various stages of the experimental gingivitis seem essentially identical to those in humans. Histologically, the appearance of the periodontium in health and disease also seems to be indistinguishable from humans. The same group of workers have also carried out longitudinal studies of experimental gingivitis over a ten-week period, six weeks longer than has been possible in humans. Histologic study of the gingiva during this period showed that the predominant inflammatory cells changed from granulocytes to lymphocytes to plasma cells, indicating that the host response to plaque may first involve non-specific inflammation, then cellular immunity, and then humoral immunity in succession. The pattern of host response exhibited in this experiment is in high agreement with less controlled studies of human beings.

Immunologic studies of macaca speciosa showed that most of the monkeys studied have serum antibody to the majority of the organisms isolated from gingival plaque material. These results agree with those from human studies of the same type. By contrast, however, studies of cellular immunity have not been exactly parallel with similar studies in humans. For example, assays of cellular immunity performed by the lymphocyte transformation method have consistently given lower values than those seen in humans. When antigens from a number of prominent periodontal organisms both from humans and monkeys were used as stimulants, the monkey lymphocytes only showed minimal transformation. The investigators are continuing their study of this problem using improved preparations of antigens.

Treatment and Prevention of Periodontal Disease

In this year's research activity on the treatment and prevention of periodontal disease, the efficacy of antimicrobial agents in preventing disease by inhibiting plaque was tested in humans and animals. Meanwhile, laboratory studies pointed to the possibility of controlling the disease by chemical interference with host mechanisms.

Earlier studies by clinical investigators at the University of Michigan's Dental Research Institute had shown that intensive topical treatment with Kanamycin for several days would protect handicapped children from signs of gingivitis for 5 weeks, even though no further treatment was given and no brushing was done. This past year, these investigators collaborated with researchers at the Plymouth Home and

Training School in Michigan in completing a one-year study of the efficacy of this Kanamycin regime. As few as 3 daily applications of 5% Kanamycin ointment on the buccal surfaces of the teeth at each 5-week period proved effective in preventing disease for 40 weeks. Bacteriology studies showed that no new bacterial resistance to the antibiotic developed during this project. The authors concluded that Kanamycin given according to the schedule described is a suitable regime to control periodontal disease in institutionalized patients unable to perform oral hygiene procedures themselves.

In human studies recently initiated at Forsyth Dental Center on periodontosis patients, investigators are testing the effectiveness of a specific regime of chlortetracycline administered systemically at a level of 1 gram each day for 10 days. After 10 days treatment is stopped, but the patients continue to be monitored clinically and bacteriologically. This treatment regime has been shown so far to arrest the disease process and to keep the patients free of suspected oral pathogens for at least several weeks.

Investigators at Loma Linda University in California have studied the effectiveness of irrigating subgingival pockets with chlorhexidine or oxytetracycline, two agents already known to prevent supragingival plaque. Using a standardized, chronic experimental periodontal pocket in dogs, the workers irrigated pockets with these antibacterial agents or with controlled solutions of saline and, subsequently, cultured the pockets. The results showed that oxytetracycline irrigation reduced the number of bacteria cultivable on the second day by 100%, and irrigation with chlorhexidine eliminated up to 90% of the bacteria. Investigators at Harvard have shown that the antibiotic actinobolin inhibits inflammation and bone loss in the jaws of rice rats when incorporated in a high sugar diet. In these experiments, this new antibiotic was found to be as effective as several other antibacterials such as penicillin, chloramphenical, and chlortetracycline. Actinobolin is of special interest to dentistry because it is poorly absorbed, nontoxic, and is not used to treat other human diseases. Thus, it possesses some of the important characteristics of an ideal drug for oral health.

On the basis of tissue culture experiments and information from the field of clinical pharmacology, grantees at Harvard University believe that aspirin may have the potential for controlling the loss of alveolar bone characteristic of periodontal disease. In the experiments, these investigators found that bone resorption due either to prostaglandin or to parathyroid hormone could be inhibited by aspirin at a concentration of 200 micrograms per milliliter. This concentration, the authors point out, is within the 150-300 ug/ml of aspirin found in the blood of arthritis patients on daily aspirin therapy. Thus, it is possible that these therapeutic levels of aspirin could be affecting bone resorption in these patients. Because of this possibility, and because prostaglandin also reduces pain and inflammation, the scientists recommend that long term studies can be done in animals and in humans to determine whether aspirin is useful in the management of periodontal disease.

In another clinically-oriented study, attention was focused on the fact that prostaglandins can cause inflammation and pain. From this study by investigators at the University of California, it appears that the principle of prostaglandin inhibition is already in use in dental practice. The study showed that several topical medicaments used traditionally to alleviate inflammation and pain in teeth and gums inhibit the local formation of prostaglandin. The authors concluded that these drugs are successful because of their effect on prostaglandin synthesis. The most potent substance tested was eugenol, a chemical agent commonly used in the treatment of periodontal disease.

Other Soft Tissue Diseases

While research on the other soft tissue diseases continues to make up only a small portion of the program, there are signs that activity in these areas is increasing. This year research activity relating to Herpes Simplex infections increased in four ongoing projects and a new grant proposal of high quality was funded. In addition, two grants seeking to discover the role of immune mechanisms in recurrent aphthous ulcers were initiated and significant findings related to oral cancer were made. Important findings were also made in *in vitro* experiments which revealed that salivary glycoproteins may protect the soft tissues of the oral cavity against bacterial adherence and subsequent infection by means of specific surface components.

The Herpes simplex virus studies included basic studies of cellular and molecular events occurring throughout the disease process as well as direct chemotherapy approaches. In an interesting study intended to throw light on the human susceptibility to Herpes infections, investigators at Duke University have measured the ability of the patient's mononuclear white cells (MNL) to undergo chemotaxis in response to the presence of viable Herpes virus. The chemotactic response of these human mononuclear leucocytes seems important because accumulation of these cells at sites of virus activity appears to be necessary before the host tissues can successfully terminate the infective process. The studies showed that viable Herpes simplex virus, but not polio or rheovirus, caused a depression of chemotactic responsiveness. These studies suggest a mechanism by which virus infections, such Herpes simplex virus infections, may depress cellular immune functions in humans and this may explain the inability of individuals with recurrent Herpes simplex virus infections to entirely rid themselves of the virus. In another study an attempt is being made to devise an effective vaccine against Herpes simplex virus. In this project, investigators at the University of Pennsylvania Center for Oral Health Research are carefully analyzing and purifying the antigens produced during infections with this virus in tissue culture. In another approach to Herpes control, a group of researchers at the University of Michigan Dental Research Institute are studying the natural history of oral and perioral Herpes simplex virus infections and attempting to discover the critical cellular and chemical events which take place between the virus and host cells. Currently, they are seeking a scientific rationale for the use of the chemotherapeutic agent known as ara-A. In

a new grant programmed by NIDR staff, other important aspects of the immunology of oral Herpes simplex virus-1 infections are being examined by scientists at Emory University. In this multifaceted study, four patterns of clinical disease will be thoroughly investigated by clinical and laboratory procedures and the therapeutic efficacy of BCG and of transfer factor will be evaluated.

In the two grants on recurrent aphthous ulcers, an investigator at the University of California and a researcher at the University of Pennsylvania are both examining the immune aspects of this common disease entity. In the project at Pennsylvania, successfully programmed by staff, the investigator will include studies of autologous lymphocytes thought to cause the ulcers by exerting a cytotoxic effect on oral epithelial cells.

Investigators at the University of Pennsylvania Dental Research Institute are studying the mechanisms by which cancerous tissue may spread from its original location in the body and cause death. In these studies the various mechanisms of spread are being examined in experimental animal systems with special emphasis on the regulatory role of the hosts' immune system. A related study by this group of researchers on canine oral tumors confirmed previous reports that the early immune response to neoplasia tends to stimulate rather than to inhibit tumor growth.

A report of a case of chronic mucocutaneous candidiasis by medical scientists at Duke University may provide a better understanding of the susceptibility of these patients. The patient, already known to show depressed delayed hypersensitivity reactions was found by the Duke investigators to also have a defective monocyte chemotactic response. Subsequent treatment of the patient with transfer factor resulted in normalization of the chemotactic responsiveness, re-establishment of the delayed hypersensitivity reaction, and a marked clinical improvement. This case is consistent with the possibility that defective immunochemotactic responsiveness may result in depressed delayed hypersensitivity, and susceptibility to fungus infections.

Earlier studies by workers at Forsyth Dental Center resulted in evidence that the ability to adhere to oral mucous membrane cells is an important factor enabling the bacteria to cause infection of these tissues. The same investigators showed in a second phase of their research that salivary immunoglobulins inhibited this adherence of bacteria to oral epithelium, and thereby were able to protect against local disease. This past year these investigators have conducted <u>in vitro</u> studies which have revealed a mechanism by which salivary glycoproteins may also protect against oral bacteria. According to the findings, the salivary glycoproteins can prevent the adherence of specific bacteria to epithelial cells because the glycoproteins have specific chemical binding sites just like those on epithelial cells surfaces. Thus the bacteria stick to the glycoprotein binding sites instead of adhering to and infecting the epithelial cells. In addition to preventing the attachment of bacteria to epithelial cells, the salivary glycoproteins were also found to cause the bacteria to separate from or desorb from cells to which they had already become attached.

MEETINGS SPONSORED

1. The program staff held a workshop entitled "Mechanisms of Connective Tissue Degradation" in Bethesda, Maryland on November 19-20, 1973. Research progress was presented in the study of proteoglycans, collagen, collagenase enzymes and elastases. It was brought out that many recent findings showing mechanisms by which inflammatory processes can cause loss of structure in periodontal disease and other diseases would not have been possible had they not been preceded by basic laboratory studies of connective tissues. It was also noted that the meeting was successful in making many competent biochemists aware of periodontal disease as an interesting area for research. A summary of the workshop and recommendations is being prepared for submission to Science for publication.

2. Under the sponsorship of the NIDR, a workshop directed to the "Problems and Perspectives of Recurrent Aphthous Stomatitis" was held in Bethesda, Maryland on December 3, 1973. The workshop brought together dental, medical and veterinary researchers who reviewed present knowledge of the incidence and severity of the disease. Recent advances in clinical pathology, immunology, virology and microbiology related to the disease were presented with emphasis on particularly promising areas of research. Deliberations by the participants resulted in the identification of efforts according to their relative importance to the control of recurrent aphthous stomatitis.

3. A workshop entitled "Immunological Mechanisms in Periodontal Diseases," was held at NIH on March 4-5, 1974. This meeting brought together leading scientists from the United States and Europr to discuss the most recent research data and hypotheses relating periodontal disease and immunological processes. The participants were in agreement that the evolution of the periodontal lesion involved progressive cellular and connective tissue developments up to and including bone loss. Other aspects of periodontal disease were presented and discussed. It was generally agreed that the disease appears to be plaque-associated, and that both cellular and humoral immunity processes are involved. Discussions also centered on the early events of the disease and agreement was reached that this is probably associated with cellular immunity (delayed hypersensitivity). However, the advanced or chronic destructive lesion is predominantly characterized by an infiltration of the tissue with plasma cells. It was also noted that periodontal disease is not a unique immunological phenomenon since the process is quite similar to other chronic inflammatory disease, such as rheumatoid arthritis and chronic glomerulonephritis. There was also considerable discussion of the mechanism of stimulation and inhibition of osteoclastic resorption of bone and destruction of collagen fibers. Since there was inadequate time for the group to analyze the findings presented during the first two days of the meeting, an additional one-day session was held approximately one month later. At this session a small group of participants deliberated on the earlier proceedings and made specific recommendations for future research to be supported by the NIDR Extramural Programs.

4. A two-day workshop on the role of dento-bacterial plaque in oral disease was held at Airlie House in Airlie, Virginia on May 21-22, 1974. At the meeting fourteen invited participants, including two foreign scientists and three NIDR staff, took part in discussions on the morphology, chemistry; microbiology, and pathogenicity of dental plaque associated with caries and periodontal disease, and on the use of animal models for studying these diseases. New evidence suggesting that different forms of periodontal disease may be caused by different bacteria was discussed by the group and the idea that there may be a certain specificity in the bacteria associated with periodontal disease was accepted by some participants as a working hypothesis. Insofar as caries etiology is concerned, the workshop discussions gave strong support to the case implicating Streptococcus mutans as a cause of smooth surface caries. During the sessions on animal models, it was brought out that both rodents and primates were extremely valuable for oral disease studies. The advantages and limitations of these experimental models were discussed and a set of guiding principles for their optimal use was agreed upon. The final summary of the workshop deliberations will be published in the open literature.

5. The Periodontal Diseases Advisory Committee held its third meeting on October 16-17, 1973, immediately following the Dental Caries Program Advisory Committee (DCPAC) meeting. In a special joint session, members of both of the above committees explored ways in which the two committees could cooperate. The main portion of the Periodontal Diseases Advisory Committee meeting consisted of a discussion of the Periodontal and Soft Tissue Diseases Extramural Program and a session on chemotherapy for oral health. In the first session the status of grant-supported research in periodontal disease was described and plans for the future were outlined. In the discussion, committee members expressed concern that heavy emphasis is devoted to basic research, while little support is given to clinical studies. In the second session, the feasibility of initiating research on the controlled release of drugs for oral health was examined. To set the stage for discussion, the following presentations were given: Dr. Hazen Baron (Warner Lambert Laboratories) "Drug Delivery System for Oral Health in the Past and Present;" Dr. J. M. Goodson (U. California at San Francisco) "Principals of Controlled Release and Potential Intra-oral Application;" Dr. Donald Cowsar (Southern Research Institute) "Current Application of Controlled Release in Other Fields of Biology." After some debate, the committee took the view that NIDR should encourage trials using the controlled release principle.

6. The fourth meeting of the Periodontal Diseases Advisory Committee, held on February 27, 1974, consisted of two sessions. At the first session, staff speakers presented material of both general and specific interest to the Committee. Dr. Frew outlined the administrative structure of the National Caries Program and drew attention to the four research strategies this program has developed. In reporting on intramural activities, Dr. Mergenhagen said that a new laboratory of oral microbiology and a new clinical component had been formed. He also described current studies on bone and epithelium. In regard to extramural research, Dr.

Goggins reported that the funding of grants related to periodontal disease had improved as a result of the recovery of the impounded money of 1973, and the release of FY '74 budget funds. Dr. Hisaoka then reviewed the history of NIH and NIDR involvement in research training from 1948 to the present. The second session of the meeting dealt with the importance of connective tissue research to periodontal disease. Dr. Piez gave a historical account of collagen research during the last two decades, and told of NIDR's strong support of this field. Dr. Lazarus then reported on the recently held connective tissue degradation workshop. In doing so, he provided the committee with an excellent review of research progress in the study of proteoglycans, collagen, collagenase enzymes and elastases. The committee members were pleased with the presentations and recommended continuation of studies of the type described by the speakers.

Seminars.

During the Spring of 1974, the program arranged four seminars on research related to periodontal disease. In one seminar, Dr. S. S. Socransky of Forsyth Dental Center presented new findings (cited earlier in this report) on the role of specific oral bacteria in the etiology of periodontal disease, with special reference to potential pathogens in periodontosis. The subject of another seminar by Dr. Martin Levin of the University of Washington at Seattle was the role of bacterial products in periodontal disease. A presentation by Dr. Bernard Guggenheim of the Institute of Dental Research at the University of Zurich described new findings from gnotobiotic animal studies in which experimental periodontal disease was caused by one or more known organisms working together. In a comprehensive seminar on potential immune mechanisms of bone resorption in inflammatory periodontal disease, Dr. John Horton of the Walter Reed Army Institute of Dental Research and Dr. Ann Sandberg of the NIDR Intramural Program presented new material on both the humoral and cell mediated aspects of localized bone resorption.

FUTURE PLANS

Continued emphasis will be placed on defining the numerous steps of the disease process in periodontal disease and in oral soft tissue lesions, in order to develop more rational means for their prevention and control. Thus, ongoing and new studies will attempt to develop both practical and fundamental knowledge on all of the biological events involved in these disease processes from the earliest attachment of bacteria to the tooth or tissue to the ensuing immune inflammatory responses associated with tissue destruction or pain. Because adherence of bacteria to teeth or to soft tissue is important in initiating infection, special emphasis will be given to this area. In view of the recent isolation of new organisms highly suspected of being periodontal pathogens, studies will be done to characterize these organisms and relate them to disease. Meanwhile, efforts to clarify the role of immune mechanisms in periodontal and soft tissue diseases will continue,

as well as specific studies on the biochemistry of periodontal connective tissue components. Research to identify and test various chemotherapeutic agents for efficacy in preventing plaque or inhibiting bone resorption will also be sustained and expanded.

Increased programming efforts will also be made to stimulate research dealing with aphthous ulcers, herpes virus infections, and oral cancer. In particular, research will focus on the development of better diagnostic methods for herpes simplex virus infections and on the search for suitable treatment methods for this disease. In addition, research efforts will continue on the virology and immunology of this disease, with the objective of developing a vaccine for ultimate prevention. Extended emphasis will also be given to the problem of oral cancer. In order to develop a more cohesive program in this important area, continuing effort will be made to coordinate NIDR activities with those of the regional cancer centers and other programs of the National Cancer Institute.

SUMMARY

The Periodontal and Soft Tissue Diseases Program fosters research related to periodontal diseases, oral ulcerative diseases, oral cancer and other oral soft tissue disorders. Since these diseases involve complex biological processes, the program supports research and research training efforts in a wide variety of fields. During the past year research funds totaling approximately $5 million were awarded to support 5 program projects, 76 research grants and one international symposium. Approximately 85% of these funds went to studies of the periodontal diseases. The program also provided approximately $2 million for the support of 97 trainees on 25 training grants and for 52 postdoctoral awards of various types. During the year staff made visits to more than thirty institutions to program, monitor, or to evaluate proposals for research or research training. Staff also participated in 7 scientific meetings and in 3 formal professional development courses.

Among the research highlights of the past year were additional findings to support the contention that there may be bacterial specificity in the etiology of periodontal disease. Studies of the rapidly destructive condition called periodontosis have implicated a particular group of Gram-negative organisms as possible causative agents in this severe form of periodontal disease. These organisms are suspected because they were isolated from the sites of greatest disease activity in patients, they produced extensive periodontal bone loss in gnotobiotic animals, and their elimination from diseased human pockets by mechanical and antibiotic therapy caused the disease to be arrested.

Studies to elucidate the bone resorption of periodontal diseases have shown that the bone resorption factor associated with cell mediated immune inflammation requires cooperation between two types of inflammatory cells. It was also shown that the bone resorption factor produced by these cells is similar to but not identical to parathyroid hormone.

Other studies of bone resorption indicated that humoral immunity mechanisms with the aid of the complement system can cause local bone resorption.

Studies of the interaction between the host and organisms associated with periodontal disease showed that two organisms known to induce the disease caused leucocytes to release potentially destructive lysosomal enzymes without involvement of antibodies. Related studies showed that similar enzymes were not overtly destructive to epithelial cells but caused the cells to be disrupted from their attachment surface, a finding of possible significance in the pathogenesis of gingivitis. Elegant studies on the cell biology of chronic inflammatory disease revealed evidence that sensitized lymphoid cells release substances which damage fibroblasts, the cells which produce collagen fibers and other structural elements of connective tissues. In complementary studies, it was also shown that activated lymphocytes also produced substances which cause macrophages, the large white cells which engulf foreign materials, to release biochemical substances capable of causing connective tissue degradation.

Because of the occurrence of serum antibody to periodontal organisms and the presence of immunoglobulins in gingival tissues, it is believed that antigen-antibody complexes play a role in human disease. New evidence supporting this concept came from studies this year showing that several immunoglobulin and complement components were present in inflamed gingiva in a bound form. Studies of the chemistry of the gingival fluid of patients with periodontal disease were consistent with this concept.

In this year's research on the treatment and prevention of periodontal disease, the efficacy of antimicrobial agents in preventing disease by inhibiting plaque was tested in humans and animals. Kanamycin alone was shown to protect handicapped children from gingivitis for nearly a year. As few as 3 daily applications given every 5 weeks proved effective in preventing disease for as long as 40 weeks. Two studies on the effectiveness of chlortetracycline and of chlorhexidene in inhibiting subgingival plaque seem encouraging, but the results remain preliminary. The antibiotic actinobolin was shown to inhibit periodontal disease in rice rats, but no further information on the clinical potential of this agent seems to be evolving, in spite of its highly favorable characteristics for oral use. Continuing studies on bone resorption involving inhibition of prostaglandin synthesis have led to the speculation that aspirin might be useful in the management of periodontal disease. Since the blood levels of aspirin found in arthritis patients frequently reaches levels that can inhibit bone resorption in tissue culture, some researchers recommend that clinical studies of the aspirin effect be conducted immediately.

Research activity relating to Herpes Simplex infections increased significantly and efforts to discover the role of immune mechanisms in recurrent aphthous ulcers were resumed. Important findings were also made in <u>in vitro</u> experiments which revealed that salivary glycoproteins

may protect the soft tissues of the oral cavity against bacterial adherence and subsequent infection by means of specific surface components. The salivary glycoproteins apparently prevent the adherence of bacteria, because the glycoproteins have specific binding sites just like those on the epithelial cells. Thus the bacteria stick to the glycoprotein binding sites instead of adhering to and infecting the epithelial cells.

Program staff sponsored three high level workshops on periodontal disease mechanisms and one on the status of recurrent aphthous stomatitis research. Subjects discussed at the periodontal disease workshops were: mechanisms of connective tissue degradation; immunologic mechanisms in periodontal disease; and the role of dentobacterial plaque in oral disease. Eminent scientists from all parts of the world particpated in these meetings. As summarized in the text of the report, staff also participated in the development of three meetings of the Periodontal Diseases Advisory Committee, and in the presentation of four seminars on research related to periodontal disease.

Future plans call for continued emphasis on defining the numerous steps of the inflammatory disease process with special attention to the relationship of inflammation to both soft and hard tissue destruction. Studies to identify effective preventive measures will be expanded and efforts to stimulate research on aphthous ulcers, Herpes infections and oral cancer will be increased.

Prepared by A. A. Rizzo

ANNUAL REPORT FY 74

CRANIOFACIAL ANOMALIES PROGRAM

INTRODUCTION

The Craniofacial Anomalies Program supports research and research training related to the etiology, pathology, prevention, and treatment of craniofacial malformations. Included in the program are studies in (a) congenital malformations such as cleft lip/palate and other syndromes which may involve several craniofacial structures; (b) acquired malformations from surgery or accidents; and (c) malocclusion of teeth and jaws. To develop a broad base of knowledge helpful in clinically oriented projects, the program supports fundamental research in prenatal and postnatal developmental biology. The general research plan to address these deformities involves three categories of research: first, the systematic identification of the affected populations and the investigation of the factors associated with the development of the malformation; second, the development of experimental model systems to investigate the biologic characteristics of the defect with a view towards preventive programs; third, clinical studies to improve the clinical and biologic classifications of the abnormalities and to improve the prognosis of children with these defects. Workshops which touch on each of these areas were held in FY 1974.

ADMINISTRATION

During FY 1974, the program expended $5.1 million for 61 research grants, which included 13 program projects, and 8 special dental awards (small grants), and one clinical research center grant. For research training the program awarded $939,000 for 16 training grants furnishing stipends for 76 trainees, and $77,000 for 5 postdoctoral fellows. Research career development awards were made to 5 individuals. Under the new Weinberger program, $455,000 was awarded to support 26 fellows on 7 institutional fellowship grants, and $161,000 was awarded for 15 individual postdoctoral fellowship awards. By means of special grant support, the Craniofacial Anomalies Program has assisted the Teratology Journal in increasing the number of its subscribers from 1,000 to nearly 1,800 within the past two years. Thus, the program has encouraged the growth of a journal which has become very important to basic and applied researchers in the field of congenital malformations. Table 1 illustrates the distribution of research support by mechanism of funding. The dollar level for FY 1974 represents an increase of approximately 24 percent from FY 1973. Table 2 illustrates the distribution of research grants according to subject area. The Craniofacial Anomalies (General) category is primarily composed of basic studies in developmental biology which are pertinent to nearly all types of craniofacial malformations. Support for cleft lip/palate research was the largest category, with 34 percent of the available funds devoted to this subject.

TABLE 1

FY 1974 STATISTICS REGARDING RESEARCH GRANTS

Total Active Research Grants	83
Grants Awarded in FY 1974	61
Terminated or extended without funds	22

ALL GRANTS BY TYPE		Active	Funded	Funds (Total Cost)
Program Projects	(PO1)	12	12	$2,894,882
Clinical Research Center	(PO2)	1	1	342,000
Regular Research Grants	(RO1)	56	42	1,812,104
Special Research Award	(R23)	12	6	51,602
Conferences	(R13)	2	--	--
TOTALS:		83	61	$5,100,588

TABLE 2

FY 1974 STATISTICS REGARDING CATEGORY AREAS

	No. of Grants	FUNDS	
		Cost	Percent
I. Craniofacial Anomalies - General	24	$1,268,008	25
II. Cleft Lip/Palate	24	1,737,209	34
III. Other Congenital Anomalies	8	1,030,792	20
IV. Malocclusion	27	1,064,579	21
TOTALS:	83	$5,100,588	100

STAFF ACTIVITIES

Program staff made visits to 16 universities to discuss with grantees and potential grantees the various mechanisms of extramural programmatic support, or to assist in the assessment of the state of the art in craniofacial anomalies at the field level. Staff also participated in 12 NIH workshops or conferences, four of which were initiated and organized by the Craniofacial Anomalies Program, and served as staff observers at more than 20 study section site visits to review research grant applications.

In addition, staff consulted with international scientists at 11 scientific congresses or meetings on craniofacial biology, orthodontics, cleft palate, and birth defects. These meetings presented an opportunity to confer with the renowned authorities in each of the malformation fields and served as a resource in programmatic planning. Advancements in animal model systems, immunogenetics of congenital anomalies,

mechanisms of teratogenesis, and early diagnosis of malformations were a few of the highlighted areas.

The following list identifies these congresses and meetings:

1. Teratology Society Meeting, Montreal, Canada, June 1973.

2. Third International Meeting of the Craniofacial Biology Group (IADR), London, England, August 1973.

3. Third International Orthodontic Congress, London, England, August 1973.

4. Second International Congress on Cleft Palate, Copenhagen, Denmark, August 1973.

5. Fourth International Conference on Birth Defects Vienna, Austria, September 1973.

6. American Speech and Hearing Association Convention, Detroit, Michigan, October 1973.

7. American Dental Association's 114th Annual Meeting, Houston, Texas, October 1973.

8. International Association for Dental Research, 52nd Annual Session, Atlanta, Georgia, March 1974.

9. American Cleft Palate Association Annual Meeting, Boston, Massachusetts, April 1974.

10. The Sixth Annual International Biomaterials Symposium, Clemson, South Carolina, April 1974.

11. American Association of Orthodontics Annual Meeting, Houston, Texas, May 1974.

RESEARCH HIGHLIGHTS

A. Mechanisms of Normal and Abnormal Growth and Development

Recent advances in the field of biochemistry at the University of Southern California include the generation of significant data regarding intercellular interactions, cell-extracellular matrix interactions and the consequences of these interactions upon biosynthetic processes. For example, in examination of mechanisms of intercellular interactions during embryonic mammalian tooth formation it was discovered that matrix vesicles containing RNA may mediate the transfer of developmental information between tooth epithelium and adjacent tooth mesenchyme. These studies also showed that both tissues synthesize collagen. However, recent data indicates that the type of collagen synthesis is different.

The experimental approach of forming teeth by tissue recombinations amongst mouse-rabbit, mouse-chick, and several different species of mice provide a new method with which to "engineer" enamel and dentine formation and alterations in tooth design. In this method, referred to as intraspecies chimera formation, embryonic primordial tissues are excised from a donor animal and transplanted into a new environment in a recipient animal. The main advantage the method offers is to allow separation of genetic factors and the microenvironment, so that information genetically coded in the cells can be revealed more clearly. It now becomes feasible to design tooth properties conceptually and then to select specific species and specific tissues within animals and with which to form these special teeth. For example, it may be possible to combine in one new tooth, enamel with the properties of rat incisor enamel, and dentine with the properties of rabbit premolar dentin.

One parameter of cell-extracellular matrix interactions can be investigated by examining how the microenvironment of a cell modifies or influences the cell's abilities to synthesize tissue-specific types of collagen. Such studies at the University of Southern California have recently shown that in osteoarthritis, cartilage cells which normally secrete $(\alpha 1)_3$ collagen begin to synthesize skin-type collagen $(\alpha 1)_2\alpha_2$. This change in genetic expression is mediated by changes in the microenvironment of these cells. It has been demonstrated that lysosomal enzymes *in vitro* can cause modifications in gene expression as evaluated by collagen specificity. These recent advances by these investigators are providing valuable information related to fundamental processes associated with craniofacial development.

Investigators at the University of Southern California have just demonstrated by immuno-cytochemical methods that histocompatibility alloantigens are located on the outer cell surfaces of both tooth epithelium and adjacent mesenchyme during early embryonic tooth development. With immunofluorescence it is possible to visualize cell surface H-2 antigens on each of the tissue types; therefore it becomes technically possible to determine if membrane associated materials are transferred from one cell type to another during development. Further, this technique enables the visualization of either tissue type associated with intraspecies tissue recombinations. Numerous processes in development associated with intercellular interactions, including cell migrations, cell recognition, cell-cell fusions, cell-matrix interactions, are all believed to be mediated at the outer cell surface. Therefore, studies of the structure and function of cell surfaces are fundamental to many problems in craniofacial developmental biology. Ongoing projects of this type include studies to examine intraspecies and interspecies tooth formation *in vitro*, and to reveal the mechanisms of intercellular communication between dissimilar tissues such as epithelium and mesenchyme.

Genetics plays an important role in the formation of congenital craniofacial anomalies. In basic studies to improve our understanding of how genetic transcription is controlled in chromatin, investigators are attempting to learn the role of non-histone proteins. A central question is whether the non-histone proteins which can be isolated from the chromatin are transported into the cells, into the nuclei and into the chromatin in an undegraded form. If these non-histone proteins are revealed to be regulatory proteins, it may then be possible to relate a genetic abnormality to a lack of a specific regulatory protein, and utilize this information for treatment or prevention.

B. Cleft Lip/Palate

Embryology: Two exciting developments in the current research at Michigan State University on the mechanism of cleft palate formation utilize the same experimental technique in which mouse embryos are immersed in a synthetic fluid while they are still attached to the maternal organism by the umbilical cord. In this technique, the spinal cord of the pregnant mouse is transected at T3, rendering the abdominal area insensitive, the animal is half immersed in fluid, and the embryos are released from the uterus into the bath of synthetic fluid. Working with embryos in this bath during the time the palate might be expected to close, investigators observed that the palate did progress from the open to the closed position. Using this system to study the mechanisms of cleft palate in mice with a genetic prediliction towards clefting, the Michigan State investigators found that removing the tongue at the beginning of the experiment caused the number of cleft palates to be reduced. This finding suggests that the tongue may normally interfere with palate closure.

The same technique was then used to study the mechanisms by which cortisone induced clefts experimentally in mice. In these cortisone experiments there were also considerably fewer open palates when the tongue was removed and considerably more clefts when the tongue was left intact. Thus, cortisone appears to interfere with tongue displacement from between the palatal shelves rather than with the fusion of the palatine shelves after the tongue is out of the way. In previous work also related to palatal closure, investigators in this laboratory showed that muscular movements of the embryo are the most probable cause of tongue displacement normally, and such movements are greatly reduced in cortisone-treated mice. Therefore, it is likely that cortisone causes cleft palate in mice indirectly by depressing the activity of the neuromuscular system in the embryo.

The foregoing paragraphs described studies which suggest that cortisone or glucocorticoids may delay shelf movement and cause cleft palate by inhibiting the tongue musculature. In complementary investigations at Children's Hospital Research Foundation in Cincinnati scientists are addressing the possibility that contractile components within the palate itself might also be involved in shelf movement.

In studies reported last year, these investigators had demonstrated active synthesis of an actin-like protein in palates and in addition a myosin-like component. In more recent studies, they have shown that the rates of synthesis of these contractile proteins in palate were equal to or greater than that observed in the tongue, a finding consistent with the possibility that these contractile elements may contribute to shelf elevation. It was also noted that when embryos were immersed in d-tubocurarine, a muscle inhibitor, palatal shelf rotation was blocked. This result also indicates that muscle contraction is involved in palate shelf rotation, but still leaves in doubt the exact role of contractile proteins actually within the palate, since the contractile muscle(s) may reside outside of the palate.

In another laboratory approach to cleft palate research, an organ culture technique approximating in utero conditions and capable of supporting the process of palatal shelf elevation and fusion has been devised at the University of Michigan. In this technique, embryonic mouse heads can be maintained in a unique culture chamber for periods up to 5 days, and the entire process of secondary palate formation may be studied. Utilizing this in vitro system, experiments are in progress to investigate the role of various craniofacial features in palatal shelf closure. Experiments conducted so far indicate that palatal shelves apparently require both an intact maxillary-mandibular complex and space in the oral cavity, which is provided by tongue removal, to achieve the closure process. It is possible that normal mandibular growth or normal tongue activity may provide the space in developing embryos. The results of this study thus coincide well with findings described earlier in this report on the important role of the tongue in palatal shelf elevation.

One general assumption of investigators studying the development of the secondary palate of mammals has been that connective tissue cells from each palatal process migrate across the midline and that this migration effects the union between these separate tissue masses. The assumption has been tested at the University of North Carolina by in vitro combinations of palatal processes in which the cells of one of the palatal shelves could be distinguished from the cells of the other. When the cells of one process were labeled with tritiated thymidine prior to in vitro growth, subsequent autoradiographic studies indicated that "fusion" of palatal processes does not involve movements of significant numbers of mesenchymal cells from one palatal process to the other. Cellular transmigrations cannot, therefore, account for the formation of an effective union between palatal processes.

Investigators at the University of Southern California are studying the interaction of genetic and in utero environmental factors by a special technique in which mouse embryos of one strain are being implanted into a foster mother of a different strain of mice. By this technique, the influence of the maternal environment on the susceptibility and incidence of cleft palate formation is being examined

in two mouse strains (AJAX AND C57) which manifest dissimilar spontaneous cleft palate incidences.

The broad and comprehensive research programs on cleft palate also include studies on subhuman primates. A recent report from workers at the University of Washington describes their 4-1/2 year old M. mulatta male, who has a complete unilateral cleft palate. Until recently the breeding capabilities of this extremely rare animal were doubtful, and the investigators had not been able to involve him in breeding experiments. However, it was observed that he has now mated successfully and an early aborted embryo was produced. Although the embryo was too young to show anomalies of the craniofacial complex, the breeding capabilities of the male are assured and studies will continue.

Also at the University of Washington retinoic acid, an oxidative form of Vitamin A, was used for the first time to produce a cleft of the soft palate in the monkey. Additional deformities were noted in the limbs, heart, and lungs while the mandible was noted as being very small.

2. Epidemiology - Genetics

An interracial comparison was made on the incidences of isolated cleft palate, and cleft lip with or without cleft palate in Hawaii. The incidence of cleft palate was relatively uniform among racial groups except Hawaiians and part-Hawaiians, who are at higher risk. For cleft lip, the incidences are 1.05 per 1,000 births in Caucasians and 1.92 in Japanese. Generally higher incidences were observed among Orientals especially Japanese, Filipinos, and Chinese. No maternal or hybridity effects were detected. There was no evidence of marked degree of dominance or recessivity for either defect in the data. In studies by the University of Minnesota of 3,200 Haliwa Indians in North Carolina it was found that the incidence of cleft palate or lip and palate was one in 56 births, at least ten times higher than the U.S. average. A kindred charting of all clefts in this population showed that every person with a cleft was related to one woman who was born in 1832. While it is accepted that cleft palate is generally determined by polygenic factors, data from this study indicates that there is a major dominant gene concerned in the production of certain types of cleft lip and palate.

At Indiana University the sex ratios were studied in individuals with cleft lip and cleft palate who have a near relative also affected. It is known that the overall sex ratio in the total population of clefts of the lip with or without clefts of the palate to be 2/1, male to female. However, this average figure does not adequately represent the sex distribution within individual families. For example, the sex ratio of probands (affected individuals) in a given family is reduced to approximately 1.4-1 when they have an affected parent of either sex. Surprisingly, when an aunt or uncle is the

closest affected relative to the proband, the sex ratio of those probands within a family is approximately 3.5-1. These data seem to be inconsistent with predictions of the polygenic model and need further clarification.

3. Psychosocial

The psychosocial impact of the cleft lip/palate lesion on the infant, child and adult provides many research questions. At the University of Iowa it was noted that children with cleft palate may demonstrate considerable withdrawal behavior and somewhat lower educational achievement in the preteen years. While there was no direct evidence from this project that these effects of the cleft are permanent or handicapping, studies to identify special periods of social-educational deficiencies in these children will continue because they might lead to more effective counselling of these patients and their parents. Meanwhile, in a study of adults with cleft lip/palate, investigators at the Lancaster Cleft Palate Clinic have observed that cleft lip/palate subjects married significantly later and proportionately fewer males entered into marriage. This observation was confirmed by a study at the University of Pittsburgh where it was noted that only 40% of the adults with cleft lip/palate married whereas 72% of their nearest siblings did so. At Duke University the effects of cleft lip and palate on body satisfaction were examined. The study demonstrated that adults with clefts gave lower ratings of satisfaction to body parts and functions related to the clefts, e.g., lips and speech.

4. Speech

A study of cleft palate speech at the University of Iowa indicated that early diagnosis of velopharyngeal incompetence (the ability to close the pharynx with the soft palate during speech) is extremely important. The study showed that children with clefts who achieve velopharyngeal closure can improve their speech faster and with fewer lessons than cleft palate children with marginal closure. Those unable to achieve closure seem to benefit little from speech therapy. This research underscores a need for improved methods of diagnosing palatal incompetence in young children, since early identification would permit surgical correction to improve palatal function.

The possibility of modifying speech hypernasality without surgery in children with clefts is under investigation at the University of Alabama. In a preliminary study, attempts were made to make subjects aware of hypernasality and to teach them speech techniques to reduce hypernasality. Thirteen of the 20 subjects studied were able to detect their own hypernasality and achieve a reduction in this undesirable voice quality. These patients were judged to have a good prognosis for normal nasality without further surgery.

Although palatal incompetency undoubtedly contributes to speech distortions in speakers with cleft palate it is also possible that anterior deformities associated with clefting provide additional speech difficulties. A study at the University of North Carolina revealed that subjects with palatal incompetency have significantly larger oral port areas than do normal subjects or cleft palate subjects with palatal competence. It is thus apparent that not only do these patients have difficulty closing off the posterior opening of the mouth, but they also have problems in closing off anterior spaces with the tongue.

5. Surgery and Wound Healing

At Duke University significant advances have been made in the handling and treatment of the cleft lip/palate child. In severe bilateral clefts of the lip, primary repair of the lip is now deferred until there has been time for orthodontic expansion of collapsed maxillary segments and for repositioning of the premaxilla. The optimum time for the surgical repair itself appears to be approximately 12 weeks after the collapsed maxillary segments have been expanded and stabilized (about 3 months of age). The cleft lip and the associated deformity of the nose can then be satisfactorily reconstructed in one operation. In these studies it has been possible to reduce the number of operations on patients with unilateral clefts of the lip, alveolus and palate from eight to four, and the number of operations on patients with bilateral clefts of the lip, alveolus and palate from an average of twelve to six, without compromising the welfare of the patients.

Experimental animal studies at the University of Iowa indicate that simulated palatal surgery on normal animals drastically reduces skeletal growth on the operated side as compared to normal growth on the unoperated side. In additional studies on the growth role of the nasal septal cartilage, it was found that partial cartilage removal in normal young beagle dogs resulted in shorter upper and lower jaws, and an increased interocular distance. A concurrent study is being conducted to map the chondrocytic proliferation at various zones within the growing septum to explain these interesting clinical findings.

Investigators at the University of California have developed an experimental primate model with a new palatal suture so that they can study the micro-environment and discover how the alternating growth processes of suture formation and bone-induction are controlled. Successful research to elucidate the nature of these micro-environment influences could permit viable suture transplantation into the cleft in cleft palate habilitation, and provide a rational approach to the alleviation of premature closure of cranial sutures in craniostenosis.

C. Over a period of years, the University of Illinois has amassed a comprehensive series of longitudinal cephalometric data on a wide variety of syndromes to provide insight into the natural history of such deformities. These data are invaluable in developing a rational basis for

clinical management including the timing of treatment, selection of appropriate therapeutic maneuvers, and evaluation of the results of treatment.

An investigation utilizing discriminant analysis of roentgencephalometric data showed that mandibular form was syndrome-specific in the Pierre Robin syndrome. This finding suggests that the cleft palate in this syndrome may be related to the micrognathia. Since the characteristic shape of the mandible is maintained throughout the growth period of the affected individual, the mandibular form can be used as a genetic marker which may become a useful tool in family studies.

Anatomic analysis of syndromes represents a complex challenge because of the 3-dimensional distortions and the limitations of typical 2-dimensional radiography. At the University of California a system is being developed and tested for integrating data from stereo head films, stereo photographs and dental study casts to yield a single craniofacial map in which the locations of all structures are reported in terms of a common 3-dimensional coordinate system. Tests of the reliability and validity of the system are now in progress.

D. Malocclusion

1. Craniofacial Growth: Theoretically, epidemiological data on growth and on the heredity patterns of craniofacial morphology and malocclusion should have value in clinical application. However, investigators at the University of Michigan have concluded that broad parameters taken from a heterogenous population such as the U.S. population have little diagnostic significance. The best estimate of an individual's facial growth potential may be determined by examining the relatives in the immediate family. When multivariate analysis was applied to family data obtained in this manner it was revealed that correlation coefficients for 21 cephalometric variables were higher in the sister-brother than they were in nonrelated pairings. These data indicate dramatically the advantage of family data over population norms.

At the University of Oregon studies are in progress to develop equations which adequately model dento-facial growth so that adult size and form can be predicted. An intermediate step is to study individual growth data in cluster analyses. The identification of individuals of each growth cluster should aid in the understanding of his growth pattern and growth potential.

Since the maxillary suture plays an important role in the development of the width of the maxilla in children, the growth of this suture was measured. In these studies carried out at the Royal Dental College in Copenhagen, Denmark, it was found that the mid-palatal suture followed a typical growth curve with a growth spurt at 14 years of age. From 4 to 20 years of age the suture was found to grow an average of 6.3 millimeters per year. This study suggests that the

appositional bone growth contribution to maxillary width development is small in humans.

2. Biochemical and Cellular Aspects: The hypothesis that cyclic AMP is a mediator of hormonal-induced bone resorption is being tested at the University of Pennsylvania in studies on the role of this substance in the physiological bone resorption related to tooth movements and tooth eruption. Having developed a simple technique for a rapid assay of cyclic AMP, the investigators applied the method in studies of orthodontic tooth movement. Their initial data showed that predictable changes in cAMP levels occurred in the alveolar bone following the application of mechanical force. The establishment of this definite biochemical pattern in response to force application will now allow the investigation of other "first messengers," such as electric currents and prostaglandins. It is believed that studies of this type may lead to clinically applicable knowledge.

The ability to control the specific rate of tooth eruption would be extremely useful in orthodontic procedures where treatment time is delayed due to unfavorable eruption rates. In order to learn more about the rate of tooth eruption a project at the University of Maryland was undertaken to study in mice the effects of external influences such as temperature, occlusion, and physical restraints on cellular activity and the rate of tooth eruption. It was observed that there is a direct relationship between cellular activity of dental tissues as measured by DNA synthesis and occlusion. Physical restraint was shown to retard the eruption rate and cellular activity of mouse incisors, but removal of the restraint and of occlusal contact caused accelerated tooth eruption and increased cellular activity in these teeth.

At the University of Tennessee, tissue culture techniques are being used to evaluate the effects of epithelial growth factor (EGF) and mesenchymal growth factor (MGF) on monolayers of cells derived from mouse epithelium, bone and muscle. These factors, obtained from mouse submandibular salivary glands, have been shown by previous workers to produce precocious tooth eruptions and early eye opening in embryos. The influence of EGF and MGF on the development of other orofacial structures in vivo is under examination as well.

3. Biomechanics and Mandibular Function: The ability to predict the movement of a tooth under the influence of external forces is important in the treatment of malocclusion. To improve this ability, investigators at the University of Connecticut are studying the structural system of tooth, periodontal ligament and alveolar bone using experimental and holographic analytical techniques.

The study employs a double-pulse laser system to obtain "fringe" lines on the tooth. The conversion of these lines to displacement components in conjunction with the knowledge of the applied force system yields the complete force-response information necessary to yield useful clinical data. With this system it is now possible to

measure small displacements of a tooth (1-100 microns) in three dimensions of space, so that the exact direction and magnitude of displacement of the tooth under a specific force system can be determined.

The full range of mandibular function including articulation of the teeth as well as temporomandibular joint articulation is under investigation at Case Western Reserve University. The study revealed that the paths of motion of the mandibular incisor teeth in subjects with good occlusion is distinctly different from that of subjects with malocclusion, even though the paths of motion of the mandibular condyles are similar in both groups. The authors concluded that jaw motion is indeed affected by occlusion, and that comprehensive studies of jaw motion can be useful in diagnosing occlusal health. The investigators also observed in every subject tested that when the teeth made sudden contact with a hard object, all mandibular movement stopped immediately. Since other parts of the body normally respond to sudden pain or discomfort by a protective withdrawal reflex, the jaw freeze response noted in these studies may represent a unique feature of oral physiology. In the same investigation, findings were also made concerning temporomandibular joint (TMJ) pain, one of the most difficult dental problems to manage. It was noted that most of the subjects who exhibited TMJ pain and crepitus (joint sounds) also demonstrated considerably more mandibular mobility. Correction of the malocclusion in these patients reduced the pain but did not alter the condylar mobility.

4. Treatment Studies: It has been noted in previous studies that mechanical expansion of the maxillary arch also produces anatomical changes in the nasal structures. In recent studies at the University of North Carolina nasal function was tested in patients in whom the upper jaw had been expanded maximally, and who had subsequently sustained a certain amount of relapse in the maxillary expansion. The tests revealed that there was a decrease in air flow resistance in the nasal airway at the time of maximal jaw expansion followed by an increase in resistance when the maxillary relapse had occurred.

Removable activator appliances have been used for many years to treat malocclusion without careful documentation to show how these appliances change dental and oral structures. In a nearly completed study to evaluate activators, scientists at the University of California can now report several observations. According to the authors, the appliance directly affects tooth position by contacting the teeth and indirectly affects tooth position through changes in the adjacent musculature. Secondly, even though the activator holds the mandible forward there is no apparent effect on mandibular length. Thirdly, the activator appliance is apparently of greatest value in treatment of malocclusions in the transitional dentition, before the malocclusions become manifest in the permanent dentition. It was also noted that children who were mouth breathers did not respond as favorably to the use of the appliance as did nasal breathers. This observation reflects the complex relationship between tongue, dentition

and oral function in the presence of an oral airway. Animal experiments are currently under way to test specific hypotheses regarding mandibular posture and nasal airway obstruction.

MEETINGS SPONSORED:

1. Neurosurgical Problems in Craniofacial Habilitation - Bethesda, November 5, 1973. This meeting was designed to identify and discuss the neurosurgical and post-operative problems arising from craniofacial surgical procedures which warrant investigation.

   RECOMMENDATIONS:

   a. Research is needed to identify the cause(s) of craniostenosis.

   b. The brain-dura-skull tissue interrelationships need study to identify specific roles in growth control and surgical alteration of the cranium.

   c. The role and properties of the dura should be identified in adults during and after different stages of maturation.

   d. Investigations on mechanisms of sutural and endochondral growth should be promoted.

   e. Research is needed to determine the most effective way to perform surgery on craniofacial bones without interfering with the growth processes.

2. Developmental Biology and Craniofacial Anomalies - Bethesda, November 13, 1973. This meeting was designed to involve developmental biologists in the problems of craniofacial malformations. These investigators will hopefully add a new dimension to research in this field and perhaps they will recognize specific anomalies as good model systems for the study of developmental processes.

   RECOMMENDATIONS:

   a. Research is needed to focus on the timing and biological clocks of developmental processes.

   b. The role of the basement membrane as a functional biological structure needs study.

   c. The roles of innervation and vascularization in developmental processes require investigation.

   d. Information is vitally needed on synchronization of many developmental processes as cell migration and aggregation.

   e. The field of limb-bud research may offer research methodology applicable to craniofacial anomalies research.

f. Development of animal model systems compatible to human understanding is indicated.

3. Surgical Research Problems in Craniofacial Habilitation - Bethesda, November 21, 1973. This meeting was designed to identify and discuss oral and plastic surgical problems arising from surgical procedures which warrant investigation.

RECOMMENDATIONS:

a. Improvement in the nomenclature and classification of congenital malformations is needed.

b. Behavioral studies are needed to assist in the decisions of surgical timing and patient management.

c. Biological mechanisms of muscle reattachment and migration needs investigation.

d. Biomechanical research related to fixation of anatomical components during healing is indicated.

e. Pre- and postoperative innervation and vascular changes require detailed study.

4. State of the Art Workshop - Research on Craniofacial Orthopedics - Bethesda, February 12-13, 1974. This meeting was designed to involve expert researchers in such fields as craniofacial growth and development, orthodontics, bone biology, and orthopedic surgery in an assessment of the state of the art of research in the utilization of orthopedic forces for correction of craniofacial malformations.

RECOMMENDATIONS:

a. The process of control systems in morphogenesis needs investigation, such as feedback control chains, bioinduction and bioelectric phenomena.

b. Biomechanical principles of nonmineralized tissues; i.e., periosteum in growth, ligaments in articulation, muscle migration, and response of collagen to stress need description.

c. It is timely to foster detailed study of malformations regarding pathogenesis of conditions, such as hemifacial microsomia, and to correlate the form and function of these malformed structures.

5. Research on Mandibular Function and Dysfunction, Buffalo, New York, April 25, 1974. This meeting was designed to examine the highly coordinated activities of the stomatognathic system and the state of identification and classification of the pathologic conditions that are of concern to dentistry.

6. The Second International Congress on Cleft Palate, Copenhagen, Denmark, August 26-31, 1973. Partial support was given to this international meeting which included the most recent advances in clinical and laboratory research of cleft lip/palate as well as other congenital craniofacial anomalies. The meeting was well attended and world-wide in scope.

FUTURE PLANS

During FY 1975 the Program will sponsor workshops in: (1) Craniofacial Anomalies Classification and Nomenclature, (2) Psycho-Social Aspects of Craniofacial Malformation, and (3) Research on Orthognathic Surgery. The workshop on classification and nomenclature deserves special mention. The goals of this workshop will be to develop a model which will promote uniform and biologically meaningful terminology within the field of malformation communication. At this stage of craniofacial research there is a special need for such efforts, because progress in developing new concepts and new knowledge is being hampered not only by a lack of understanding of morphogenesis but also by imprecise language and uncoordinated classifications. The term "funny looking kid" syndrome serves as an example of the totally inadequate terminology which appears all too frequently in the current literature. It is anticipated that the workshop participants will produce a relatively simple model of classification and nomenclature.

While giant steps have been made in embryology, nevertheless, the precise timing of various stages of cellular differentiation and migration has not been determined in human development and, consequently, many questions related to the morphogenesis of craniofacial anomalies still need to be answered. Cultivation of mammalial embryos of animal models in vitro should now make it possible to perform studies in experimental embryology as the next step to follow the investigations on embryonic migration of labeled cells from the neural crest in chick. Experimental studies conducted at this stage of development should help to reveal differences between such cartilaginous growth centers as nasal capsule, Meckel's cartilage and the cranial base.

To remedy the defects caused by craniofacial malformations, scientists in the past have attempted to induce desirable skeletal remodeling by chemical, mechanical or bioelectric methods. Progress in this approach has not been great because the field has been hampered by a lack of understanding of the mechanisms of the biologic effects induced. However, recent advances in biochemistry of bone metabolism suggest that controlled induction may now be possible, if the appropriate biologic signals can be invoked. Therefore, studies to understand the mechanisms of these signals and the corresponding responses will be expanded so that the clinical control of bone growth and repair may become a reality.

During FY 1975, new studies will examine the role of vascularization during craniofacial development, the process of epithelial fusion, when the palatal shelves contact, and the phenomena of cell recognition and programmed cell death during palatal morphogenesis. Studies will

also be initiated to identify the critical alterations in neuro-muscular activity which produce dento-skeletal alteration and malocclusion in response to pathologic stimuli. Such studies should offer insight into potential mechanisms of malocclusion development. The concept of Craniofacial Anomalies Research Centers to achieve a cohesive effort in investigations of the severe congenital craniofacial anomalies will continue to be explored. During FY 1975, special efforts will also be made to program postdoctoral fellowships to train researchers in all aspects of this broadly based field.

SUMMARY

The Craniofacial Anomalies Program supports research related to the oral cavity, face and cranium. Program funds are provided not only for projects on congenital and acquired malformations and malocclusion of teeth and jaws, but also for fundamental research in prenatal and postnatal developmental biology. In FY 1974, over five million dollars was awarded for 61 research grants or programs. This is compared to less than four million dollars in FY 1973.

This report describes studies which relate cell biology, immunology and biochemical genetics to the morphogenesis of oral structures. In these investigations, intercellular interactions in tooth formation have been demonstrated both biochemically and in vitro. Evidence was also obtained that information may be transferred between the epithelial and mesenchymal layers of a developing tooth via the RNA-containing matrix vesicles which were localized in one investigation. Further support for intercellular communication has been obtained through in vitro tissue recombination techniques in which teeth with predetermined structural characteristics were cultured from selected samples of tooth epithelium and mesenchyme. Other projects dealt with the means by which cellular microenvironment and regulatory proteins control cell function.

New developments in cleft lip and palate research have resulted from a diverse group of projects. Secondary palate formation has been observed experimentally in exteriorized mouse embryos which are still attached to the maternal organism. The technique permits direct observations on the effects of teratogenic drugs such as cortisone on palatal closure and tongue displacement. The data obtained with cortisone administration suggested that cortisone produces cleft palate in mice as an indirect result of reducing the neuromuscular activity of the embryo and thus hindering the normal displacement of the tongue from between the palatal processes. Other organ culture methods have also been developed to study the processes of palatal shelf elevation and palatal fusion in intact or dissected embryonic mouse heads.

The genetic components in the etiology of human cleft lip and palate were followed in epidemiological studies involving racial groups in Hawaii, in a high risk Haliwa Indian population in North Carolina, and in another population in which the afflicted person was studied within individual family groups and sex categories. It was found that a major dominant gene

may be involved in the production of cleft lip and palate in the Haliwa Indians since every person with a cleft was related to one woman who was born in 1832.

Studies on surgical intervention and wound healing in cleft lip/palate patients have given new emphasis to procedures that minimize iatrogenic reduction of growth. Other experimental data indicated that simulated palatal surgery on normal animals drastically reduces skeletal growth on the operated side as compared to the unoperated side. Another group of experiments on the basic mechanisms of bony suture formation has opened up the possibility of developing an effective biological habilitation measure. The procedure envisioned would involve the surgical placement of viable bony sutures in areas where sutures are missing (cleft palate), or where sutures have prematurely closed (Apert's Syndrome).

Research in malocclusion encompassed both laboratory studies on the basic cellular response to orthodontic treatment and clinical projects on craniofacial growth and oral function. Attempts to define the fundamental stimuli involved in bone formation and resorption have shown that cyclic AMP may mediate a signal in mechanically stressed bone. Another project with potential clinical application looked into factors controlling the rate of tooth eruption. By altering the occlusion or by applying physical restraints, the rate of eruption of mouse incisors was accelerated or slowed.

Projects concerned with craniofacial growth prediction, biomechanics, and treatment evaluation have improved the diagnosis and treatment of orthodontic problems. One study concluded that the best estimate of a patient's facial growth potential may be determined by examining relatives in the immediate family rather than relying on population norms. Another important investigation evaluated orthodontic treatment using the activator appliance. It was found that the activator is most effective in treating malocclusions when used during the transitional dentition. Apparently, the activator repositions the mandible without inducing an increase in growth of the mandibular length.

Drafted by R. L. Christiansen

ANNUAL REPORT FY 1974

RESTORATIVE MATERIALS PROGRAM

INTRODUCTION

The consequences of oral diseases are damaged tissues. Until these diseases are eradicated there will be a need for materials to repair these tissues and to restore function and appearance. Thus the major objective of the Restorative Materials Program is to develop new and improved materials for better treatment of dental and oro-facial disorders. The second objective is to develop materials and devices for the prevention of oral diseases. To achieve these objectives, research support by both grant and contract mechanisms is furnished to a variety of investigators in the physical and biological sciences.

The program supports research in five broad categories: (1) Filling materials, including alloys and composites for repairing damaged teeth; (2) Bonding agents, including adhesive coatings and cements for protecting the surfaces of teeth against decay and for sealing the margins of fillings; (3) Maxillofacial prostheses for replacing tissue defects resulting from birth defects, surgery, or accidents; (4) Artificial tooth implants to provide replacements for missing teeth or anchors for bridges and dentures; (5) Miscellaneous studies on toxicity, standards, equipment, and devices designed to improve dental care.

Since the program is intended to support a balanced slate of projects in restorative materials covering all essential aspects of the field, the opinions of an expert ad hoc Materials Advisory Panel was solicited this past year to aid in developing favorable program balance. Their recommendations are outlined later in this report. In general, the panel recommended that the program should attempt to develop and maintain balance by stimulating contract activity in special areas whenever needed. During the past year this principle has been put into practice in the implant and in the maxillofacial areas, where new contracts have been let to fill voids in the research being done in these areas. The studies on implants are attempting to determine both the relative efficacy of the materials (metals, ceramic, plastic, glass and carbon) as well as the importance of root designs in the acceptance of the implants. In the projects on maxillofacial prostheses, contractors will develop and test materials specifically for use as artificial skin in humans.

Since it has been observed in humans that tooth implants often seem acceptable for short periods of time, but subsequently become loose, the studies initiated by the program this past year will be continued for 3 years. Staff recognizes that the future course of research on tooth implants will depend upon the outcome of present studies and those already

planned. At the moment, there seems to be a critical need to properly evaluate implants which are free standing (not splinted) and under functional stress. Such studies are planned for the coming year. These studies should also reveal the advantages of certain animal models in translating findings on experimental implants to the human.

ADMINISTRATIVE

Table I shows the distribution of funds for research grants, contracts and interagency agreements in FY 1974. Expenditures of $1.2 million were made for 32 grants and $0.7 million for contracts and interagency agreements. Approximately one fourth of the total funds were expended for research to improve or develop new filling materials, about one fourth was spent to continue projects dealing with adhesives, and about one fourth was spent on implant investigations. About 18% of the funds were allotted to studies on prosthetics and the remainder went to general research. For research training the program made awards totalling $555,000 to support 8 training grants which provided stipends for 34 trainees. Under the new Weinberger program, 2 individual postdoctoral fellowships were awarded at a cost of $21,000.

Table I: FY 1974 Distribution of Research Funds

Program Interest	Grants (32)	Contracts and Interagency Agreements (7)	Total
1. Filling Materials	$493,000	-	$493,000 (25%)
2. Bonding Agents (coatings, cements)	184,000	$217,000	401,000 (21%)
3. Prostheses			
a. Facial	53,000	187,000[1/]	240,000 (12%)
b. Oral	111,000[2/]	-	111,000 (6%)
4. Implants	245,000	284,000[3/]	529,000 (28%)
5. General	150,000	-	150,000 (8%)
Totals	$1,236,000	$688,000	$1,924,000

1/ Includes 60% of 2 1/2 year commitment of $195,000.

2/ Includes FY 1974 share of a multi-year funded grant (3502).

3/ One-third of 3 year commitment of $839,000 + $4,430 extension.

STAFF ACTIVITIES

Program staff visited 18 institutions for the purposes of programming, monitoring, or evaluating research grants, research training grants or contracts. In addition, staff participated in 14 scientific meetings in which program plans for research accomplishment were discussed. Through these professional activities, staff was able to keep abreast of developments and to help define future directions for research progress in this field. A list of these activities is given below:

a. Dental School Visits

University of Pittsburgh	Sept. 1973
Virginia Commonwealth University	Nov. 1973
University of the Pacific	Dec. 1973
SUNY, Stony Brook	May 1974

b. Site Visits - Grant Applications

(1) Training:

T01 DE 189	Polytechnic Inst. of New York	Feb. 1974
T01 DE 127	Georgia Tech., Atlanta	March 1974

(2) Research:

R01 DE 3504	Emory Univ., Atlanta	March 1974
R01 DE 0433	Univ. of Indiana	April 1974

c. Site Visits - Contractor

NIH-NIDR-71-2383	Midwest Research Inst.	Aug. 1973
NIDR-NIDR-71-2386	Battelle, Northwest	Oct. 1973
DE-32422	Harvard Univ.	Nov. 1973
DE-32420	Clemson Univ./Med. College of Georgia	Dec. 1973
DE-32421	U. of Florida	Dec. 1973
DE-40015 (Interagency Agreement)	Nat. Bureau of Standards	Feb. 1974
NIH-NIDR-70-2238	Franklin Research Inst.	March 1974

d. Site Visits - Contract Proposals (Maxillofacial Prosthesis)

U. of Alabama, Birmingham
A. D. Little Co., Boston, Mass. Jan. 1974
Union Carbide Corp., Buffalo, N. Y.

e. Meetings and Conferences

(1) Navy Technical Workshop on Dental Research (Bu. Med. and ONR) Warrenton, Va.
(2) NIDR Symposium on "Dental Biomaterials-Research Priorities" Chicago, Ill. August 1973

(3) Federal Materials Seminar, New York, N.Y.	Sept.	1973
(4) American Academy of Perio., San Antonio, Texas	Oct.	1973
(5) ADA Convention, Houston, Texas	Oct.	1973
(6) NYU Dental Adhesive Mat. Conf., N.Y., N.Y.	Nov.	1973
(7) ADA Materials Council, Chicago, Ill.	Dec.	1973
(8) IADR, Atlanta, Ga.	March	1974
(9) NIDR Implant Symposium, Atlanta	March	1974
(10) Clemson Symposium on Biomaterials, Clemson, S.C.	April	1974
(11) Seminar on Oral Implants (Brookdale) N.Y., N.Y.	April	1974
(12) NSF Biomaterials Res. Rev., Hartford, Conn.	April	1974
(13) ADA Materials Council, Chicago, Ill.	May	1974
(14) Ed. Workshop in Periodontology, Durham, N.H.	June	1974

f. Courses

Project Officers Course, Hershey, Pa.	Oct.	1973

RESEARCH HIGHLIGHTS

The program is currently funding nine studies on endosseous tooth implants. In these studies experimental implants of several designs fabricated from several different materials are being tested in baboons, dogs and swine. The designs range from solid blades to porous tooth root replicas, and the materials include polymethyl methacrylate, calcium aluminate, vitreous carbon, "bio-glass" and titanium. Since most of these studies are still in the early stages, no findings from these projects can be reported at this time. However, progress can be reported from research efforts initiated earlier. Investigators at the University of Illinois have obtained evidence that specimens of sintered titanium wire in the shape of cylinders have remained firm for up to 24 months after implantation in the mouths of baboons. In another study supported by contract at Battelle Northwest Laboratories in Richland, Washington, it was shown that porous metal composite implants made of Titanium-Aluminum-Vanadium in a cylindrical form were successfully retained in the mandibles of swine.

Since the research supported by contract during the past few years on marine adhesives has not shown promise of yielding a material useful in dentistry, such studies will not be continued. While these studies have contributed interesting information on the biochemistry and the physical properties of the proteinaceous cementing substance of barnacles and mussels, retention tests indicated that these cement secretions are no better than synthetic products already available. The original goal of this research was simply to test the feasibility of deriving a useful product from knowledge of marine adhesives, and the results have been negative. Thus, staff feels that the goal of the research effort on this question was accomplished, and that the decision to discontinue this line of investigation is now based on valid scientific evidence.

A National Bureau of Standards interagency agreement has shown progress in standardizing a laboratory procedure for measuring the potential functional wear of restorative materials. This work is significant because it may enable scientists to accurately determine the wear characteristics of new materials without having to resort to long term, expensive clinical testing.

MEETINGS SPONSORED

1. A grant was made to Clemson University for partial support of the Sixth International Symposium on "Materials for Reconstructive Surgery" held at Clemson University April 20-24, 1974. This meeting was one of a series of high level annual conferences regularly attended by a variety of active investigators interested in biomaterials and implantation. Those who participated included physicists, chemists, ceramicists, engineers and metallurgists, orthopedic surgeons, thoracic surgeons, plastic surgeons, and dentists at the fore-front of this expanding field.

2. A staff-initiated Symposium/Conference entitled "Dental Biomaterials Research Priorities" was held in Chicago on August 7-9, 1973. As indicated in last year's annual report, the 2-day symposium consisted of four half-day sessions covering each of the following subjects: Restorative Dentistry; Protective Coatings; Maxillofacial Prostheses; and Implants. The programs included formal papers by experts and sufficient general discussion so that the participants could analyze the current status of the fields, identify important gaps in knowledge, and recommend avenues of research. More than 200 research leaders contributed to this endeavor. Following the Symposium, an ad hoc Materials Advisory Panel conferred to discuss the information gathered from the Symposium, to evaluate its significance and to recommend future goals and priorities for the next several years. This special advisory panel was composed of ten outstanding research leaders from the fields of materials science and prosthetic dentistry.

The full proceedings of the 3-day Symposium/Conference were published in February, 1974 as DHEW Publication No. NIH 74-548, which was subsequently distributed to all attendees and other interested parties. The following list of items was taken from the publication and is included here to summarize the specific recommendations made by the Materials Advisory Panel regarding future research. The Panel recommended:

1. Long-term clinical performance evaluation studies of accepted and new filling materials;

2. Investigations on non-precious alloy casting metals and on the technology for their investing and casting;

3. Studies to develop molecular adhesive systems to prevent microleakage and plaque adherence;

4. Studies to strengthen composite coupling systems to optimize their physical properties and minimize wear;

5. Studies to develop maxillofacial and soft liner prosthetic materials;

6. Projects to standardize evaluation criteria for comparing the results of dental implant studies; and

7. Experimental trials to establish an animal model system for predicting human dental implant results.

SUMMARY

The primary objectives of the Restorative Materials Program are to develop new and improved materials for better treatment of dental and orofacial disorders and to develop materials and devices for the prevention of oral diseases. The program supports research in five categories: (1) Filling materials, (2) Bonding or adhesive agents, (3) Prosthetic materials, (4) Artificial tooth implants, and (5) Miscellaneous studies including toxicology and materials standardization. During FY 1974, $1.2 million was awarded for 32 grants and $0.7 million for contracts and interagency agreements. In addition, the program made awards totaling $555,000 to support 8 training grants and $21,000 was awarded for 2 individual post-doctoral fellowships.

The opinions of an expert ad hoc Materials Advisory Panel were solicited this past year to aid in developing a balanced materials program. Recommendations of the panel supported program efforts to develop contracts in areas requiring increased research. Such an area of priority is that of maxillofacial materials where, in the past year, 2 contracts were awarded to develop new skin materials for maxillofacial rehabilitation.

Research in materials was highlighted this past year by successful activity in dental implants. Porous endosseous implants in cylindrical form fabricated of titanium wire have remained firm in baboon jaws for up to 24 months. In another study, cylinders of a porous metal composite of titanium, aluminum and vanadium were successfully implanted into the healed tooth sockets of miniature swine. In standardization studies, progress was made in developing procedures to measure wear in restorative materials. Contract research on marine adhesives was terminated after several years of research had shown little possibility of yielding an adhesive useful in dentistry.

The Program aided in the sponsorship of two important meetings. A grant was made to partially support the highly successful Sixth International Biomaterials Symposium entitled: "Materials for Reconstructive Surgery," held at Clemson University in April 1974. A staff-initiated symposium entitled, "Dental Biomaterials Research Priorities," was held in Chicago in August 1973. More than 200 researchers attended this meeting.

ANNUAL REPORT FY 74

MINERALIZATION, SALIVARY SECRETIONS AND NUTRITION PROGRAM

INTRODUCTION

The Mineralization, Salivary Secretions and Nutrition Program supports basic and applied research efforts designed to expand knowledge of (a) the role of nutrition in the growth, function and health of the craniofacial complex; (b) the normal structure and function of salivary glands and their secretions; and (c) the mechanism of the mineralization process. Under the present guidelines, only undifferentiated research is assigned to this program area, the targeted research on mineralization and salivary secretions being administered in the more disease-oriented extramural programs.

ADMINISTRATION

During FY 74, the program made awards for 37 research grants totaling $2.1 million. Funds awarded for mineralization research were slightly over $1.4 million for 21 grants, and funds for basic studies of salivary glands and their secretions (17 grant awards) totaled just over $0.5 million. During the year, six new applications dealing with salivary gland secretions were approved, but only three were funded. In addition, two grants concerned exclusively with nutrition were supported at a combined level of $55,000 per year.

Staff efforts to implement the recommendations made by an *ad hoc* advisory committee in late FY 73 (described in the Future Plans section of this report) were successful in reducing total new support for grant projects dealing with inorganic calcium phosphates by approximately one-half million dollars. The actual reduction reflected in the FY 74 program budget amounted to $352,000, since three new grants in the area of mineralization research were funded. It should be noted also that despite the decrease in total funding in FY 74, the number of active grants on mineralization increased from 23 to 26; ten of these grants deal with inorganic calcium phosphate structure and chemistry. Program staff will continue to monitor these grants carefully with the full intention of shifting the program emphasis towards more biologically oriented studies.

For research training, the program expended $464,000 to make awards for 7 training grants which support 34 trainees, and $20,000 for the support of 2 special fellowships. The program also supported 1 career award and 2 career development awards at a cost of $82,000. Most of the training grants emphasize hard tissue research, but one is concerned with metabolism and nutrition. Under the new Weinberger program, $33,000 was awarded for one institutional postdoctoral fellowship grant supporting 2 fellows, and $95,000 was provided for the support of 8 individual postdoctoral fellows.

STAFF ACTIVITIES

During the year staff made visits to institutions for the purpose of monitoring and evaluating on-going research supported by NIDR as well as to determine the feasibility of initiating research or research training in a given area. In addition, visits were made to program research grant proposals in identified areas of need. Staff also attended several scientific meetings where both programmatic and monitoring activities were engaged in. These visits and meetings are listed below by category.

Monitoring, Evaluation and Programming

1. Cornell University, Hospital for Special Surgery project site visit, November 5-6, 1973.

2. Downstate Medical College of New York at Brooklyn, program visit, November 6, 1973.

3. School of Dentistry at Stony Brook, Department of Oral Biology, programming visit, November 7, 1973.

4. University of Washington, Center for Research in Oral Biology, project site visit, April 30-May 3, 1974.

5. University of Iowa, nutrition contract negotiation, May 29-30, 1974.

6. University of Pennsylvania, two project site visits, May 30-31, 1974.

7. University of Washington, nutrition contract negotiation, June 5-7, 1974.

Scientific Meetings

1. Gordon Research Conference, Teeth and Bones, Meriden, New Hampshire, July 8-13, 1973.

2. Workshop on Mineralized Tissues of Interest to Dentistry, Sun Valley, Idaho, August 6-10, 1973.

3. Gordon Research Conference on Food and Nutrition, New London, New Hampshire, August 6-10, 1973.

4. Conference on Obesity sponsored by the Fogarty International Center, Bethesda, Maryland, October 1-3, 1973.

5. American Dental Association, Houston, Texas, October 29-November 2, 1973.

6. Workshop on Carbohydrates sponsored by the Nutrition Study Section, Bethesda, Maryland, January 16, 1974.

7. American Association of Dental Schools and the International Association for Dental Research meetings, Atlanta, Georgia, March 18-24, 1974.

8. Conference on The Development of Sweet Preference, Fogarty International Center, Bethesda, Maryland, June 19-21, 1974.

Staff Development

1. NIH Collaborative/Extramural Program Retreat, Airlie House, July 11-13, 1973.

2. NIDR Retreat, Washingtonian Motel, Gaithersburg, Maryland, September 6-7, 1973.

3. Executive Committee on Extramural Affairs Seminar, Dulles Marriott Hotel, February 26-27, 1974.

RESEARCH HIGHLIGHTS

Mineralization

Studies by investigators at the Dental Research Institute at the University of North Carolina, cited in last year's annual report, had developed evidence that there are distinct differences between hard and soft tissue collagen. These investigations were based upon the stabilization of the collagen molecules through cross-linking as indicated by reductions with tritiated borohydrate (sodium borotritide, Na^3H_4). In this reaction the amount of tritium label indicates the number of reduced aldehydes hydroxynorleucine and dihydroxynorleucine. Extension of these studies during the present project period have confirmed that the distribution of the cross-links in dentine collagen as compared with tendon collagen is different. These studies suggest that cross-linking as well as other recognized characteristics of collagen, such as organization and packing of fibrils, are all under very fine biochemical control.

In a companion study, these investigators found that reduced aldehydic cross-linked precursors (mentioned above) in collagen molecules of bovine fetal skin and tendon change in relation to each other as the collagen matures. In the fetal state the collagen molecules of these tissues contains a substantial proportion of hydroxynorleucine, but only traces of dihydroxynorleucine. However, as the collagen undergoes maturation to adult collagen, the proportion of dihydroxynorleucine increases greatly.

In a previous report results were presented which indicated that fluoride could be manipulated to enhance both penetration and accumulation in enamel.

Recent studies by a grantee at the National Bureau of Standards have attempted to define the optimal conditions for forming dicalciumphosphate dihydrate, a compound which reacts readily with fluoride to form fluoroapatite. Fluoroapatite is the crystalline tooth mineral which is believed makes enamel resistant to decay. This approach to topical fluoride application eliminates the disadvantages of surface etching and calcium fluoride formation. Plans are currently being made to identify a suitable in vitro or animal experimental model system for testing the anticaries effect of the fluoride incorporated into the enamel by these methods. It is recognized that the anticaries effect of fluoride is not necessarily related to the actual amount in the tooth. Since this system incorporates the fluoride into the enamel in relatively high amounts and at a considerable depth in a stable form, it is very important that anticaries activity be tested.

In a companion study of enamel solubility these same investigators have made a significant contribution to our understanding of the carious lesion. During this project period the researchers improved methods for measuring the solubility of a single tooth surface and subsequently carried out repeated equilibration studies on six individual teeth. They made the following observations: (1) the solubility of the enamel surface was always higher than that of synthetic apatite; (2) although a large range of solubilities was observed, differences between teeth were much greater than the differences within a single tooth; and (3) there was evidence that the mineral in the external surfaces was less soluble than mineral from the deeper layers of enamel. The authors concluded that the differences in solubility between teeth may account for variations in caries experience exhibited by different teeth, and that the low solubility of external enamel surfaces may explain why in the early carious lesion the external surface remains intact while subsurface layers are completely demineralized.

Since increased levels of the enzyme carbonic anhydrase are associated with parathyroid induced bone resorption, it has been hypothesized that parathyroid hormone operates through mechanisms involving carbonic anhydrase. Further evidence to support this hypothesis was presented by a grantee working at the University of Louisville. Meanwhile, grantees at the Pennsylvania State University have developed a fluorescent labeled antibody technique to assay carbonic anhydrase at the cellular level and have used it to obtain findings which support the earlier work. Using this method, they have detected carbonic anhydrase in osteoclasts, in shell gland cells, and in red blood cells in the chicken. The amount of carbonic anhydrase in osteoclasts is sufficient to be of physiologic significance and therefore the results support the hypothesis that at least some aspects of bone resorption involve carbonic anhydrase.

In studies on bone resorption inhibitors, grantees at Boston University have continued their exploration of compounds which lower serum calcium and phosphorus and inhibit resorption of bone stimulated by parathyroid hormone. Thus far, two of the active compounds are 5-methyl-2-thiophenecarboxylic acid and its slightly more potent analog 5-brom-2-thiophenecarboxylic acid.

These studies indicate that these compounds have an inhibitory effect on erythrocyte carbonic anhydrase. Future studies to understand their mechanism of action will include experiments with prostaglandin (PGE_2) which has been shown to stimulate bone resorption in cultures and is also found in inflamed gingiva of patients with periodontal disease.

Bone rebuilding studies have been continued through a collaborative effort between investigators at the Boston University and the University of Illinois. It was reported last year that these studies involve the use of decalcified allogeneic cortical bone matrix (DABM) to replace alveolar ridges in endentulous dogs, to fill surgically-created bone defects around roots of teeth and to replace defects in long bone. This easily-handled implant material apparently induces new bone growth and then becomes resorbed itself, being entirely replaced by new bone. In the present project period, fluoride and estrogen were examined for possible effects on the ability of DABM to stimulate new bone growth. It was found that neither fluoride supplementation nor estrogen influenced the osteogenic response to DABM. Ovariectomized rats without supplementation of estrogen did not show a diminished response, and the administration of estrogen to intact rats did not enhance osteogenic response as measured by the serial radiograph method of monitoring new bone formation.

Studies in which DABM was used to replace joints gave encouraging results. In experiments on one-day old rats, the investigators successfully replaced the condylar portion of the mandible with DABM. This resulted in the development of a new condyle similar to the control condyle in shape but slightly smaller in size. Mandibles with new condyles whose formation had been stimulated by DABM were significantly longer than mandibles from which the condyles had been removed but not replaced with DABM. The formation of the new condyle appeared to allow the mandibles to function normally and the mandibular midline became properly aligned. By contast, when the condyle was not replaced by the osteogenic material, occlusal function was markedly disturbed and the mandibular midline was shifted to the side of condylar removal. In another experimental model, the head of one fibula, including part of the diaphysis, was removed in young adult rats and replaced with DABM. After ten weeks, the newly formed bone resulting from the osteogenic activity of DABM was similar to the fibular head of a sham-operated leg. Postmortem studies revealed that the DABM had stimulated new bone formation which joined the fibular diaphyseal fragments and produced a new fibular head complete with metaphysis and epiphysis. Furthermore, the newly formed fibular heads were not pathologically fused to the tibia or femur, and the joint space also appeared normal.

In separate studies, investigators at Duke University, the University of South Carolina and the University of Colorado have successfully used invertebrate mineralization systems to clarify cellular aspects of the mineralization process. For example, studies at Colorado have demonstrated intracellular nucleating vesicles in the jelly fish statolith. This discovery will now allow researchers to conduct valuable morphological and chemical studies which would not be possible in higher organisms. At the University of South Carolina, studies on larval shell formation in the

American oyster show that the cell cytoplasm near the hinge region contains significant amounts of calcium, a finding which suggests that the cell is active in calcium transport associated with mineralization. A special advantage of this system is that it allows investigators to observe phase differences in accumulation and release of calcium by individual cells.

At Duke University, a marine alga which undergoes calcification has been under investigation. These studies have shown that the cells can be reversibly inhibited from calcifying by calcium transport inhibitors such as lanthanum and ethacrynic acid, and also by inhibitors of protein synthesis. Although the changes in cell ultrastructure brought about by these inhibitors are not yet understood, the important finding at this point is that the cells involved in mineralization are reversibly inhibited by specific agents.

Salivary Secretions

At Temple University, scientists have explored functional and structural changes in the salivary glands of mice after a single injection of isoproterenol. Such treatment causes marked stimulation of DNA synthesis and cell division, especially in the parotid and submaxillary glands. In last year's report the investigators had described the stimulating effect of isoproterenol on ribosomal RNA synthesis. During the past year progress in this field has been so productive that it is possible now to piece together in a logical sequence the early steps occurring when the parotid glands are stimulated to proliferate. The first step appears to be stimulation of the synthesis of nonhistone chromosomal proteins in the cytoplasm of the cell, followed by migration of these proteins to the nucleus where they activate the genome. Genome activation, in turn, results in changes in the cell membrane causing a glycolipid material to be synthesized there. Glycolipids are of great concern because they become altered during cell transformation whether it is due to normal growth, viral infection or malignancies. Subsequent to the changes in the cell membrane, a second round of nonhistone chromosomal protein synthesis occurs. This is followed by a peak of ribosomal RNA synthesis, the appearance of key enzymes and the subsequent replication of DNA histones and finally cell division.

Various approaches have been used to investigate the biochemistry of the mouse parotid gland as related to the control of cell proliferation. In one of these experiments cyclohexamide, an inhibitor of protein synthesis, was found to stimulate the synthesis of nonhistone chromosomal proteins which ultimately resulted in an increase in chromatin template activity. These experiments provide an independent example of the consequences of nonhistone chromosomal protein stimulation. In another series of investigations these same scientists have investigated the effect of urethane on several steps occurring in the prereplicative phase of the isoproterenol stimulated mouse parotid. The results indicate that urethane acts at the level of DNA synthesis itself and has no effect on any of the prereplicative

steps of the cell cycle, thus providing a molecular probe to dissociate events occurring in the prereplicative phase from the DNA synthesis itself.

In addition to causing alterations in the protein of salivary glands, isoproterenol has also been shown to cause changes in inorganic chemistry. At the University of Alabama, a grantee has been studying the regulation of electrolyte transport in the duct system of salivary glands as affected by isoproterenol. He has demonstrated that marked changes in sodium and potassium occur in the duct system of the submaxillary gland under the influence of the beta adrenergic agent isoproterenol. Prior administration of a blocking agent (propranolol) suppresses the effect of isoproterenol on ductal absorption of sodium. Calcium has also been implicated as a factor in regulating flow and salivary composition especially when beta adrenergic agents are used to stimulate secretion. Those effects which have been delineated thus far suggest that calcium is part of a chain of events involving enhancement of adenylcyclase which ultimately affects secretion of zymogenic protein. For regulation of the protein secretion, calcium must be provided to the acinar cells on the serosal side. However, in the duct system it has been discovered that calcium at the luminal surface acts to regulate electrolyte transport within the duct itself. For example, lowering calcium at the luminal border of cells in the main excretory duct enhances sodium absorption even in the absence of autonomic stimulating agents. Hence, calcium secretion at the acinar cell level may actually regulate the concentration of other electrolytes in the final saliva.

Two investigators at the University of Washington in Seattle are carrying out related studies on isolated parotid acini in controlled culture systems in order to determine both biochemical and morphological responses to regulatory agents such as isoproterenol. The results are very promising in that cinemicrography of this functional unit of tissue can show certain aspects of the secretory process in vitro which cannot be determined by other methods. For example, only this time photography method can demonstrate the dynamics of membrane activity as shown by the continually changing lumen profile. This longitudinal data, in conjunction with cross-sectional data of the acinar lumen enlargement, provides a good basis for understanding the activity of membranes in the secretory process and for appreciating the energetics of membrane synthesis and involution. Such studies of secretion have been correlated with cross-sectional biochemical studies and with in vivo studies of stimulated secretion in rats. On the basis of how individual acini respond under direct observation, disparities between the tissue slice systems and the live animal systems can be reconciled. In these systems the message to secrete appears to be received differently. In the living system the message appears to be received by the entire cell population simultaneously, whereas in tissue slices the message is recognized by some cells immediately and by others at later times. While isoproterenol (ISP) treatment is known to cause morphologic and biochemical changes in rat salivary gland, there has been little effort to relate the changes in the gland to changes in the secreted saliva. Therefore, University of Alabama scientists initiated a study to compare the alterations in saliva with changes in morphology of rat submandibular gland

following high ISP treatment. It was found that saliva obtained one day after treatment displayed an electrophoretic pattern different from the control samples. Histologically, these glands showed large acinar cells filled with light staining, electron lucent granules, whereas control glands were composed primarily of terminal tubular cells and immature acinar cells. Both the electrophoretic pattern and gland morphology reverted to normal within 17 days after cessation of treatment. These results suggest that ISP treatment does not merely speed up development of the gland, but also alters it functionally.

The pH of a saliva is an important factor in oral health since variations in pH may influence the processes of microbial growth, their colonization on to teeth, and the integrity of the tooth itself. Because of these far-reaching effects, pH regulation has been under continuing study. It has been confirmed repeatedly that the bicarbonate system is the major buffering system in the saliva, but the exact manner in which this buffer is regulated has not yet come to light. In relatively recent studies, it has been found that the levels of bicarbonate secreted could be elevated either by electrical stimulation of the chorda tympani nerve or by the intra-arterial infusion of either acetylcholine or isoproterenol. With present technics, however, experimental means either to counteract or to potentiate these elevations have failed. Therefore, investigators plan to develop new technics involving isolated gland preparations in the hope of discovering measures to control the bicarbonate buffering capacity of salivary secretions.

It was reported last year that scientists at the University of Wisconsin and Boston University had identified two new groups of proteins from human saliva samples. One group is rich in proline and contains significant amounts of glutamic and aspartic acid, and the other is composed of basic amino acids. It had already been reported that the group of basic proteins exhibits genetic polymorphism, a term which means that the proteins may be present in many forms in different individuals, and may even be absent. In a collaborative effort between the two institutions it was demonstrated that the proline-rich proteins also demonstrated genetic polymorphism and that both groups of proteins are the expression of co-dominant genes. Another interesting finding was that gene frequency giving rise to these proteins are different for Caucasians, Blacks and Orientals. These two new groups of proteins are unrelated to protein phenotypes of other genetically determined blood groups and salivary secretory factors studied to date.

In an important study dealing with the response of the parotid gland to x-irradiation a grantee at Temple University, School of Dentistry, has observed that parotid gland cells are extremely sensitive to relatively low doses of radiation. This is of concern since the salivary glands are in the path of x-rays in many diagnostic procedures, and since individuals who have undergone radiation therapy to the head and neck for cancer suffer extensive salivary gland damage which ultimately results in xerostomia and dental caries. At the level of radiation given (500R) only subcellular damage is observed with no evidence of either cell death or multiplication.

Nevertheless, in examining this response it was discovered that protein synthesizing structures are damaged, that a prominent lysosomal system develops, and that there is a delay in the reaccumulation of secretory enzymes in the acinar cells after secretion. While the parotid gland has been classified from earlier research as a radio resistant structure, the present findings indicate that unsuspected changes in gland function could result from radiation.

Scientists at the University of Washington have discovered that a component of human parotid saliva is capable of inducing increased capillary permeability in rabbits. The component appears in the acid protein fraction of saliva and is resistant to boiling and to freezing and thawing. These studies may be of importance in rheumatoid arthritis and in Sjogren's syndrome since both of these conditions are associated with elevations of acidic proteins in the parotid saliva.

Nutrition

Investigators at the University of Alabama Institute of Dental Research showed in earlier experiments that under-feeding rats during gestation and lactation not only stunted the growth of the pups but also increased their susceptibility to caries later in life. These studies suggested that protein deficiency coupled with increased sugar consumption might account for the increasing incidence of tooth decay in populations throughout the world. In the early experiments the total amount of the nursing mother's milk was reduced, but dietary variables other than protein consumption were not monitored. To obtain better dietary controls, new studies were designed. In these more recent experiments, rat pups were hand fed a protein-adequate diet while others were fed a diet with equivalent calories, vitamins and minerals but low in protein. After weaning, all animals were given a protein-adequate diet which included enough sugar to promote caries. This experimental design separated the effects of protein from those of caloric malnutrition during tooth development. As suspected from the previous work, the results of the new studies showed that early protein deprivation alone caused significantly higher caries rates at a later stage in life even though protein supplementation was instituted at weaning time.

In a companion study, these same investigators have examined the biochemical parameters of rat saliva under the nutritional conditions described above. Stimulated saliva was collected for uniform intervals from the rat pups born to and reared by dams fed the isocaloric diets containing either adequate or deficient protein. Saliva collected from the malnourished pups at thirty-five days of age yielded only 1/5 the volume of the controls and the total protein content of the saliva was only 1/4 that of the controls. It was concluded that both total salivary volume and protein content are drastically reduced in malnourished rats, and that these alterations may have played a role in the increased caries susceptibility observed in the earlier studies.

It has been known for some time that trace concentrations of certain elements are essential human nutrients and that trace concentrations of other elements

are toxic. In other instances, however, the same trace element can be both beneficial and/or toxic within a narrow range of concentrations. Selenium, for example, in extremely low concentrations is essential to certain animals, but in slightly higher concentrations this element is detrimental to primates and rats. To clarify the basic effects of this element, a grantee at the University of Oregon has devised elaborate studies to determine the effect of selenium on metabolic processes of tooth development and ultimately dental caries. Since selenium was found to have a marked impact on the rat's overall eating habits, food and water intake studies were designed to eliminate this influence so that the effect of selenium alone on metabolism could be determined. By a paired feeding technique, known as yoke feeding, in which control animals are forced to consume an equivalent diet in the same pattern of intake as selenium-treated animals, it was found that selenium *per se* had no effect on glycolytic and citric acid cycle intermediates when compared with the controls. Thus, the unexpected negative results obtained in these well-controlled experiments suggest that the investigators must seek other data to explain the effects of selenium.

Scientists at the University of Minnesota had obtained evidence last year that supported the concept that a true deficiency of fluoride may indeed exist. These investigators had demonstrated that progressive infertility was observed in mice on a low fluoride diet. Since the addition of fluoride alone prevented the infertility, it was concluded that fluoride is essential in the nutrition of the mouse. In a companion study the same investigators had also found that low fluoride content in the maternal diet caused mouse pups to weigh less at birth and to develop anemia during the newborn period through twenty days of age. Replenishment experiments conducted this past year showed that adding fluoride to the diet produced a significant improvement in the anemia. Since both the iron and copper content of the low fluoride diet was adequate to support normal growth, the authors postulated that optimum fluoride may in some way effect a greater utilization of iron by the hematopoietic system.

The capacity of oral mucous membranes to serve as a barrier against the invasion of microorganisms or their toxins is an important area of study, because it appears to be intimately related to the host/parasite relationships involved in periodontal disease, aphthous ulcers and other oral diseases. To develop an understanding of the effects of nutritional status on the barrier function of oral tissues, investigators at the Massachusetts Institute of Technology developed a technique for studying the dynamics of oral mucous membrane permeability *in vitro*. In the procedure, mucosal tissue is dissected from the ventral surface of the guinea pig tongue and mounted in a special diffusion chamber. Using tritiated endotoxin as the penetrating solution, audioradiographs and perfusate analyses are made to determine whether or not the solution passes through the tissue. In tests made so far, it was found that the penetration of the endotoxin was significantly greater in the tissues of animals deficient in Vitamin C than in the tissues of normal animals. These studies provide the basis for future investigations to clarify the barrier role of oral mucous membranes.

According to a report from an investigator at the Veterans Administration Hospital in Hines, Illinois, carefully controlled metabolic studies indicate that the average adult requires an intake of calcium of 800 to 1200 mg./day. This is equivalent to the calcium obtained from a balanced diet which includes 2 to 3 glasses of milk per day. An additional observation of interest was that the retention of calcium was influenced by the presence of phosphorus. For example, retention of calcium from milk which contains phosphorus was greater than it was from calcium gluconate tablets. Moreover, when phosphate was given in conjunction with calcium gluconate, the calcium retention improved and reached the levels attained with milk.

Investigators at the Dental Research Institute at the University of North Carolina have continued their work on the effect of Vitamin D on the maturation of collagen. In earlier reports they had presented evidence to suggest that the normal cross-link pattern in chick bone collagen is dependent upon Vitamin D. In recent studies they found that Vitamin D affects the reducible cross-links in chick bone collagen in a dose-related manner and causes changes in the proportion of cross-links at very early stages, before signs of inhibition of general growth and maturation are observed. These experiments have now been extended to a bone culture system in which the investigators hope to study the effect of the vitamin deficiency on collagen turnover. Preliminary data in this system are similar to that observed *in vivo*, in that the cross-link profile appears to be related to Vitamin D concentration.

In other studies relating nutrition to the formation and maturation of collagen, scientists at the University of Pennsylvania Center for Oral Health Research report that hydroxyproline-deficient collagen molecules at body temperatures appear as denatured chains rather than as the normal triple helix. These denatured molecules are secreted more slowly than the hydroxylated molecules and do not form the normal collagen fibril structure which is important to collagen's fundamental role as a structural protein in the many tissues of the body. Oxygen, iron and ascorbic acid have already been demonstrated to be cofactors in the hydroxylation process. Further studies are now necessary to determine their specific roles in this process and to identify other cofactors related to hydroxylation and/or secretion, since interference with these important steps may influence the breakdown or dysfunction of connective tissues.

FUTURE PLANS

The present section describing future program plans includes reports on two *ad hoc* advisory committee meetings, one on mineralization research and one on nutrition research. The recommendations of the *ad hoc* committee to evaluate mineralization research are outlined in this section. Since these recommendations became available earlier in the year, it has already been possible for staff to implement some of these suggestions, and these have been described in the administrative section of this report. Insofar as the advisory workshop on nutrition is concerned, the recommendations are

outlined and reference is made to specific strategies resulting in part from the workshop. Specific mention is also made of two research contracts initiated by staff as a direct result of the nutrition advisory meeting.

Mineralization - NIDR has assumed a major role for a number of years in supporting research dealing with the mechanisms of mineralization because the major oral diseases, caries, periodontal disease, and craniofacial malformations involve calcified tissues. While these efforts have significantly advanced our knowledge, the specific mechanism of the diseases of the oral cavity remain obscure and no ideal preventive measures are yet available. Because of this situation, there was concern about the magnitude of research on mineralization and its relevance to disease solutions.

As a result, a special ad hoc committee was selected last year and was asked to evaluate the importance of mineralization research and to make recommendations on the scope and balance of such research in the future. The committee considered program productivity, duplication of effort, and areas where emphasis should be increased or redirected. The final report of the committee was submitted to the NIDR Director and subsequently to the National Advisory Dental Research Council at its June meeting 1973. The highlights from that report are as follows:

1) The committee recommended a decrease and/or a redirection of emphasis in the area dealing with preparation of single crystal or polycrystalline apatites, especially studies of structure, solubility and crystal growth which are based primarily upon materials prepared under nonphysiological conditions.

2) It was recommended that future studies involving non-living systems place more emphasis on component interactions and interfaces rather than on the components themselves. One example of an important interface which requires continued study is the mineral-organic interface of the extracellular matrix of bones and teeth.

3) The committee further recommended that efforts be made to develop and investigate model mineralization systems which are based upon cellular mediation and control of the mineralization process, and that tools and methods for isolating and working with the various cell and tissue systems of interest be developed.

These conclusions were based upon the belief that the processes of mineralization and demineralization of bones and teeth, though technically extracellular, cannot be adequately studied apart from the cells which control them. Furthermore, the bone and tooth micro-environment is so complex and heterogenous that traditional biochemical and molecular biological tools are no longer appropriate. Thus, it is believed that future progress in this field will require novel approaches to the study of viable, competent, homogenous cell populations and associated extracellular

materials. Among needed areas which can specifically benefit from such studies are: a) studies of mutant systems, b) morphological studies at the ultrastructural level carried out in conjunction with correlative biochemical studies, c) studies of the molecular biology of hard tissue differentiation, d) futher investigation of developmental biochemistry of hard tissue, and e) studies of regulatory factors involved in mineralization and demineralization.

Staff progress in implementing the first recommendation is outlined in the Administrative section of this report. Meanwhile program staff are busily engaged in programming activities to enact the remaining recommendations. For example, plans are being made to conduct a state-of-the-art workshop in the area of mineralization research. It is hoped that this workshop will cover a number of aspects relating to the role of the cell in mineral deposition and resorption including regulatory mechanisms such as Vitamin D, calcitonin and parathyroid hormone; the ultrastructure of the early mineralization process; and the response of hard tissue to environmental influences, such as injuries and manipulations.

Salivary Secretion Research - Future efforts of the program in the area of salivary secretion research will be to encourage increased research activity on the role of saliva and salivary constituents in protection against oral disease. The plan is to develop a state-of-the-art workshop to consider the base of knowledge on salivary secretions in relation to oral health and to identify future application of this knowledge to clinical problems. Although there are two ongoing studies of salivary constituents, these studies emphasize physical properties rather than protective functions. There are also studies being supported by other NIDR extramural programs on salivary immunoglobulins and glycoproteins in relation to oral diseases. Nevertheless, relatively little effort is being expended in projects to study other potentially protective salivary constituents. Hence the present staff approach.

At the present time, 10 of the 16 grants on salivary studies are concerned with the morphological, chemical, and functional aspects of salivary glands. In accord with advisory opinions received this year, staff will not actively encourage expansion in these areas of research.

Nutrition - Efforts to expand nutrition research are well underway. As reported in last year's annual report, a small workshop to identify specific problems and areas of research interest to NIDR was being planned. This workshop was actually convened on January 22, 1974, and a number of observations and recommendations of importance were made. 1) The ad hoc group of nutrition experts agreed that only classical deficiency states would be expected to have specific overt oral manifestations. Nevertheless, since poor nutrition reduces the cell's capability to function in a normal manner, the lack of certain nutrients at a specific time might lead to altered development and/or function of specific structures. 2) The group recognized that considerable nutrition-oriented research is currently underway in various laboratories, but they were concerned that few if any of these projects include studies of the effects of

nutritional deficiencies on the oral cavity and its associated structures. Thus, the committee recommended that the NIDR encourage nutritionist investigators to include the oral cavity in their studies, and also encourage them to seek NIDR support for such projects when necessary. 3) It was agreed that research training would be a key factor in developing an oral-health nutrition-related research group. Therefore, the NIDR was encouraged to utilize every available resource to develop training programs for nutrition research scientists. 4) The committee suggested that workshops to identify specific areas of research be held. It is expected that these workshops would identify oral health problems which could be studied in conjunction with ongoing nutrition research efforts, and possibly might lead to collaborative efforts between basic nutrition researchers and clinically-oriented dental scientists.

Strategy for developing the nutrition aspect of the program includes efforts to program studies in the following three areas: 1) population or epidemiologic studies, 2) laboratory studies using model systems, and 3) human studies including clinical application where practical. It is believed at this time that these three areas continue to deserve attention, although it is not clear at the moment as to what balance between the three areas should be sought. The program is planning a series of workshops to develop further strategy in this area.

As an outcome of the nutrition workshop, staff prepared a request for contract proposals to study nutrition in relation to oral mucous membranes. Ten proposals were received and two contractors were selected to initiate studies beginning July 1, 1974. In these two projects the effects of protein, calorie and Vitamin C deficiencies on the oral mucous membrane of subhuman primates will be studied. Parameters to be examined include cell turnover rates, degree of keratinization of keratinizing epithelium, biochemical activity of individual epithelial cells, and certain blood studies. Support for these contracts is expected to total approximately 100,000 dollars per year per contract for a three-year period.

SUMMARY

The Mineralization, Salivary Secretion and Nutrition Program supports basic and applied research efforts of an undifferentiated character to underpin more targeted research projects administered by other program staff within the Institute. During FY 1974, the Program expended approximately $2 million for 37 research grants and $0.7 million for 8 training grants and a number of different fellowships. The bulk of the funding for both research and for research training was awarded to support grants emphasizing hard tissue research. During the year staff made visits to seven institutions to monitor, to evaluate or to program research or research training, and also attended seven scientific meetings in which programmatic and monitoring activities were engaged in.

This year's research on mineralization has shown progress in several areas. Collagen studies have indicated that the distribution of cross-

links in dentin collagen is different from that of skin. Other studies demonstrated the importance of nutrition in the formation, secretion and maturation of collagen fibers. For example, oxygen, iron and ascorbic acid were shown to be cofactors in the hydroxylation process which is necessary for the collagen to maintain normal structure, and Vitamin D was shown to be important for the development of crosslinks during the normal maturation of bone collagen. Two studies of enamel mineralization appear to have clinical implications. In one, a method is being developed to incorporate higher concentrations of fluoride into enamel mineral through the formation of an intermediate crystal. In the other study, the differential solubility of highly localized portions of human enamel in different teeth and in different individuals was reported. These findings may explain the variation in caries susceptibility observed in different teeth and in different parts of teeth. In bone studies of interest, further evidence was obtained to suggest that the enzyme carbonic anhydrase is important in resorption. In these studies, immunofluorescence techniques showed that the enzyme was actually present in the osteoclast cells which resorb bone. In a promising study with clinical overtones, it was shown that demineralized allogeneic bone matrix could be used as an inducing agent to regrow the condylar portion of the temporomandibular joint. Two studies employing invertebrate animal systems brought forth further evidence that the cells involved in mineralization appeared to control the deposition of inorganic salts as well as matrix material.

Research on salivary secretions ranged from basic studies of biochemical processes occurring in the secreting cells to applied studies of the buffer mechanisms involved in regulating the pH of the final secretion. Several studies of salivary glands explored the structural and functional changes resulting from stimulation by isoproterenol. From these studies, it now appears possible to piece together nearly all of the early steps which occur when parotid glands are stimulated by this drug to proliferate. In these studies, the importance of nonhistone chromosomal proteins and glycolipids associated with the cell membrane were brought out. In vitro studies in which parotid acinar units in culture were observed directly by cinemicrography, it was possible to examine the dynamics of membrane activity. In other studies, it was shown that isoproterenol also caused changes in the inorganic chemistry of the salivary secretions, and in the electrophoretic pattern of the proteins in saliva. In studies on the composition of salivary secretions, two new groups of interesting proteins have been discovered. The properties of one group of these proteins suggest that they may play a role in enamel remineralization and in the formation of the early pellicle which leads to bacterial plaque development. Since the other group of basic proteins has properties similar to proteins of phagocytic cells within the body, it is believed that they may possess antibacterial properties.

Nutritional studies of the past year have dealt primarily with protein deficiency and mineral metabolism. For example, scientists confirmed earlier studies indicating that protein deficiency maintained only during

gestation and lactation not only caused growth stunting, but also increased susceptibility to dental caries. The investigators believe that the mechanisms of the caries susceptibility in these studies may be related to the saliva, since they also found that the malnourished animals produced saliva which was several times less in volume and in protein concentration than the saliva of control animals. In metabolic studies in humans, it was shown that calcium retention was increased by the presence of phosphate in the diet. Meanwhile, animal studies brought forth further evidence that fluoride may be an essential dietary element during the early growth period. According to these studies a certain level of fluoride may be required for optimum utilization of iron by the hematopoietic system. In studies designed to discover the mechanism by which selenium alters the overall eating habits of rats, it was found that selenium *per se* had no effect on glycolytic and citric acid cycle metabolism.

To aid in planning future activities, staff conducted two *ad hoc* advisory committee meetings, one on mineralization research and one on nutrition research. An important recommendation by the first committee was that research on the inorganic chemistry of calcium phosphate be reduced and staff has implemented this recommendation during the year. On the other hand, the nutrition advisory committee recommended an expansion of activity and this advice has already led to the initiation of two research contracts on nutrition.

Drafted by P. D. Frazier

ANNUAL REPORT FY 74

PAIN CONTROL AND BEHAVIORAL SCIENCES PROGRAM

INTRODUCTION AND BACKGROUND

During the past year NIDR has played a significant role in revitalizing the area of pain research. Assisted by the efforts of the staff of this program, along with the cooperation of supporting NIDR staff and the aid of outside consultants, this field has now emerged from a long period of dormancy and stagnation. Advances in both the conceptual and applied aspects have stimulated renewed interest and new controversy, and the resulting ferment has led to increased efforts to understand the complex and fascinating puzzle of pain. Of special interest to NIDR are the fear and anxiety syndrome that keeps millions of Americans away from the dentist's office, the pain and discomfort associated with many dental diseases and with almost all dental procedures, and the various oral-facial pain syndromes which are poorly understood and inadequately treated. A primary aim of this program is to develop research and research manpower to create a base of information which may lead to more effective control and alleviation of the pain associated with these conditions.

In the behavioral studies component of this program area, progress in identification of key problem areas and an overview of the total NIDR behavioral science effort will be reported.

ADMINISTRATIVE

Significant staffing improvement can be reported in the Pain Control and Behavioral Studies Program area. Dr. Richard Hayes was appointed to assist the Program Chief in developing and administering the extramural components of the program. As a part of his program responsibilities, Dr. Hayes is focusing specifically on the behavioral sciences area.

Dr. Ronald Dubner, Chief of the Neurophysiology and Anesthesiology Branch of NIDR's intramural program, contributes to the development of the extramural NIDR pain program, and Dr. Edward Driscoll, Clinical Director, NIDR, also continues to provide valuable advice and support. In addition, arrangements have been made to utilize, for one year beginning July 1, 1974, the services of Colonel Robert Johnson of the U.S. Army's Dental Research Unit. Colonel Johnson has been instrumental in the past in developing pain research programs for the Army, particularly in the area of electrical anesthesia. Thus, the present staff resources of the Pain Control and Behavioral Studies program are considerably stronger than last year, a situation which augurs well for increased effectiveness in program development.

During FY 1974, the Pain Control and Behavioral Studies Program funded 9 research grants at a combined level of $404,000. One of these awards was made for an important new study at Massachusetts General Hospital on acupuncture. This study, actively programmed by NIDR staff, will examine the efficacy of acupuncture techniques in experimental and dental pain situations. Major pain research activities were also supported at the University of North Carolina Institute of Dental Research and at the University of Washington Center for Research on Oral Biology. In addition, the program supported 14 training grants at a combined level of $1,360,125. Three of these training grants focused on either pain control or behavioral science research. Fellowship support was also provided at a level of $33,916.

STAFF ACTIVITIES

Program staff visited 15 universities to discuss specific research and/or research training endeavors with investigators considering projects in either the pain control or behavioral science areas. In addition, staff members accompanied Dr. Kreshover on four dental school visits to discuss opportunities for research in pain control and behavioral science areas. Staff also participated in eight conferences, workshops and other scientific meetings at which they discussed research opportunities in the pain control and behavioral science areas. Consultation service was provided at all of these meetings, and staff made formal presentations at four of them.

One of the meetings mentioned above deserves special highlighting. NIDR provided key financial and consultative support to enable the Section on Dentistry of the American Association for the Advancement of Science to hold a Symposium-Workshop on "The Control of Pain" at its annual meeting in San Francisco in February 1974. At the Symposium, a variety of papers were presented and discussed, including one by Dr. Ganz. The program was well attended and well received, and arrangements have been made to publish the proceedings in September 1974.

Because of NIDR's prominent role in this meeting and its support last year of the International Symposium on pain in Seattle, NIDR has become identified as the key federal focus for pain research. One impact of this stimulatory activity by NIDR has been to influence a number of outstanding pain investigators to focus specifically on research problems relevant to the oral-facial area. It is anticipated that this trend will continue and become even stronger in the future.

As indicated above, NIDR was instrumental in the convening of the International Symposium on Pain held in Seattle, Washington in May 1973. The proceedings of this Symposium have now been published as Volume 4 of the Advances in Neurology series (Raven Press-NYC). The 850 page volume has been characterized as representing a milestone in pain research theory and pain therapy. It fulfills a long-standing need for

a comprehensive up-to-date summary that covers the full range of problem areas in the field of pain and is certain to have a powerful influence on the further development and progress of pain research. A serendipitous, but highly important development resulting from this conference was the unanimous agreement by the 350 participants at the Seattle symposium to establish "the International Association for the Study of Pain." This Association will function to stimulate further progress in the field, to hold international symposia and meetings, to facilitate publications of significant new information in the field, to recommend standards relating to the use of drugs and other procedures in the treatment of pain, and to consider the founding of a journal on pain research. NIDR staff will continue to play an important role in all of these activities.

RESEARCH HIGHLIGHTS

Significant progress has been achieved during FY 1973 in advancing our knowledge and understanding of pain in a number of basic and clinical areas of direct interest to dentistry. The following discussion will identify some of these advances.

Investigators at the Temporomandibular Joint and Facial Pain Research Center at the University of Illinois College of Dentistry reported significant progress during the past year in their study of the role of psychological and physiological factors associated with the etiology and treatment of the myofacial pain-dysfunction (MPD) syndrome. A better understanding has been achieved of the personality characteristics of the MPD patient and how these relate to the development of high masticatory muscle tension in these individuals. Additional evidence for the psycho-physiologic concept of the etiology of MPD has been derived from a placebo equilibration study, from investigation of short-term psychotherapy in recalcitrant cases, from epidemiologic data on awareness of pernicious oral habits and the incidence of other psychosomatic disorders and complaints, and from radiologic studies showing the general lack of pathological changes in the temporomandibular joints of MPD patients. Finally, an analysis of long-term treatment results has confirmed that the use of conservative, reversible procedures is successful in most MPD patients and would appear to be the treatment approach of choice.

Using computer summation techniques, an NIDR-supported project at the University of Washington has generated data that unequivocally documents for the first time the existence of cerebral electrical responses to tooth pulp stimulation. These responses are associated with brief, unmistakably painful sensations referred to the individual tooth stimulated. These cerebral tooth pulp-evoked potentials represent objective, quantifiable, non-verbal concomitants of central events associated with the perception of pain and as such, hold promise as a better method of investigating acute pain in man (particularly pain originating in teeth) than the subjective verbal reports by

patients that are now so heavily relied upon.

Studies on the mechanism of action of dental electro-anesthesia at the University of Louisville hold promise for the eventual utilization of this approach for dental pain relief. In this project, analgesia is produced by passing a small electric current through the teeth. These experiments indicate that the analgesic effect produced by electricity actually results from temporary, local and reversible blockage of nerve impulses, rather than from permanent deleterious effect on nerve cells, as some had contended. Now that the reversibility of this effect seems established, it is hoped that this approach can be further developed to the point of application, so that the disadvantages associated with injection of local anesthetic drugs may be reduced or eliminated.

In a comparative study, investigators at Loma Linda and Creighton Universities found that Fentanyl is a better drug for the relief of pain in ambulatory patients than the more commonly used meperidine (Demerol). In terms of analgesia alone, Fentanyl was found to be equally as effective as meperidine, but because recovery from sedation is quicker and also because there is less of a depressant effect on respiration and blood pressure with Fentanyl than with meperidine, Fentanyl is clearly preferable. Also at Loma Linda, a project designed to evaluate currently used methods of dental anesthesia has shown that no adverse cardiovascular effects were found when healthy young adults received nitrous oxide in oxygen in concentrations up to 40%.

In a study conducted at Brigham Young Unviersity, it has been demonstrated that hypnosis can be an effective dental anesthetic. Its effectiveness in reducing or eliminating pain appears to be directly related to the patient's susceptibility to hypnosis but not related to the patient's expectations of how effective it will be. Surprisingly, there appeared to be no correlation between the depth of hypnosis achieved and its effectiveness. Of the patients studied, more than 50% were satisfied with hypnosis and about one-third actually preferred hypnosis to other procedures.

At the University of Michigan, NIDR-supported research on the trigeminal system indicates that the cerebellum receives and processes trigeminal inputs. Alteration of mandibular positions was shown to change cerebellar unit firing patterns. These findings suggest that the cerebellum may play an important role in maintaining masticatory muscle splinting. Additional studies will be required to determine the effects of cerebellar outputs on masticatory motor neurons.

PAIN CONTROL EDUCATION AND RESEARCH CENTERS

During FY 1974, staff of the Pain Control and Behavioral Studies area and the Director, NIDR initiated discussions with the American Dental Association concerning the establishment of centers in dental

schools for research, research training and teaching of the total concept of oral-facial pain control. A number of meetings were held including one in which a group of selected dental school deans and experts in anesthesiology and oral-facial pain control met to explore various approaches to meet this urgent need. As a consequence of these activities, a proposal is now being developed to be submitted by the American Fund for Dental Education to the Robert Wood Johnson Foundation for possible financial support amounting to $3,750,000 over a five-year period. This effort represents a unique cooperative endeavor between NIDR and the American Dental Association working together to meet an urgent national need in dental education and research.

Funds will be requested to enable selected institutions to accomplish the following objectives:

1. To develop and establish improved means for teaching the total concept of pain control at the undergraduate and graduate levels of dental education.

2. To conduct basic and clinical research in neurophysiology, neuropharmacology, anesthesiology and psychology of relevance to oral-facial pain problems.

3. To establish effective research training programs to enable highly qualified and motivated individuals to assume key leadership roles in academic research and administration in emerging departments of pain control and/or anesthesiology in dental school environments.

OVERVIEW: BEHAVIORAL SCIENCES RESEARCH AND NIDR

Background - It is recognized that effective control of dental diseases will depend eventually on the public's acceptance of preventive public health measures and the acceptance of professional treatment. Although economic considerations are important, appropriate psychological management by the dentist is a major factor in the acceptance of dental care. Inappropriate management may result in refusal of care and the development of even greater anxiety and fear of dentistry. Uncontrolled anxiety and fear, whether iatrogenic or not, contributes to the suffering of the patient, makes management of the patient more difficult, lowers the efficiency of the dentist and often reduces the effectiveness of the care rendered. Uncontrolled fear and anxiety not only inhibits individuals from seeking necessary dental care but also has a detrimental effect on the economics of dental care by increasing the professional time required for treatment.

In addition to the psychological problems of individual patients, sociological factors exist which seem to determine attitudes toward new preventive measures and toward dental care in general. In addition,

evidence exists that there are ethnic differences in susceptibility to and tolerance of pain. Sociologic and political considerations of fluoridation have been studied and some of the results have been applied with moderate success. There have been efforts to apply mass media persuasion techniques to dental problems, but highly effective methods have not yet been developed for the use of such media.

Educational psychologists are being used with increasing effectiveness in dental education, but it appears that the emphasis has been on teaching factual information to dental students with little emphasis on the psychologic management of the patient. Dental health educational programs have been conducted in public schools for many years with a variety of teaching methods, but the long-term effectiveness of these programs has not been adequately evaluated.

Inventory of NIDR Support in Behavioral Sciences. NIDR has supported research training in behavioral sciences with training grants at the University of Houston, (now in the tenth year of support) and the State University of New York at Buffalo, (now in the ninth year of support). Graduates from both of these programs are active in behavioral research related to dental problems. One career development awardee is now in his fifth year of support, and several post-DDS fellows have also been supported. Most of these are now active in a dental environment.

NIDR research grant support in this field is limited, and only four active grants have a behavioral science component. One of these grants is supported by the National Caries Program, two by the Craniofacial Anomalies Program, and one by the Pain Control and Behavioral Studies Program. Behavioral sciences projects are not currently being supported by the other NIDR program areas, although it might reasonably be expected that behavioral sciences research might contribute information of value. Two of the Dental Research Institutes are conducting research with significant behavioral science components. The National Caries Program also supports, through the contract mechanism, three projects containing behavioral sciences components. None, however, deals primarily with behavioral sciences.

An award made this year to the University of Connecticut by the National Caries Program is specifically designed to determine the relative effectiveness of two different methods for persuading children to adopt caries preventive procedures. Total support for this three-year program is $212,000.

In a project supported by the Craniofacial Anomalies Program at Duke University, there is considerable emphasis on research on the psychological parameters of cleft palate. This project supports a psychologist for 85% of his time and effort and about 20% of the annual budget of $112,000 is devoted to the behavioral aspects.

Within the Dental Research Institutes at North Carolina and Washington, emphasis is being placed on the use of drugs for anxiety and pain control and on techniques of operant conditioning, neurophysiologic inhibitory techniques, biofeedback and distractors, all attempting to devise improved approaches to reduce and control dental fear and anxiety.

The National Caries Program (NCP) contracts supports one contract in which attitudinal surveys will be made in an attempt to elucidate the role of the practicing dentist in providing caries preventive services. Two other contracts supported by NCP incorporated multi-faceted approaches to determine the total effectiveness of combined caries prevention procedures. In the psychological components of these studies, the effectiveness of teaching oral hygiene procedures will be tested.

This survey of the behavioral science aspects of all of NIDR program areas represents the first attempt by the Pain Control and Behavioral Studies Program area, in furtherance of its overall coordinating and evaluative role in this area, to provide an overview in this field of emerging importance.

FUTURE PLANS

Pain Research. As described elsewhere in this report, marked progress has been achieved during the last year in increasing research support for meritorious projects in pain research. Efforts will continue during the coming year to maintain this momentum. Particular emphasis will continue to be given to identifying and working with pain research investigators of the highest quality whether or not they have been previously associated with dental research. Additional details are given below concerning specific plans for workshop conferences and for oral facial pain research centers. The special cooperative project with the American Dental Association will be developed further. Greater efforts will be made to work with the dental research institutes and centers to increase their involvement in pain research and behavioral studies. Manpower development will be emphasized to the degree possible with available research mechanisms and resources. Using appropriate evaluative approaches, close contact will be maintained with all pain research principal investigators to assure maximum effectiveness and highest possible productivity of their projects.

As a consequence of the uncertainties currently surrounding all NIH training programs, specific plans for future manpower development in the critical shortage areas of pain control and behavioral sciences are difficult to formulate at this time. However, recognition by NIDR of these critical manpower needs will require continuing programming efforts by staff to identify and utilize the strongest possible training environments during FY 1975.

Behavioral Studies. In the Behavioral Studies area, grant applications will be encouraged on subjects of apparent need such as the reaction of patients to dental treatment, the relation of psychologic arousal to perception of discomfort and pain, methods of predicting arousal, methods of reducing arousal in the normally apprehensive patient, and methods for managing extremely apprehensive patients. In addition, other program areas will be encouraged to develop studies of the behavioral aspects of particular dental problems. This program will furnish consultation for these individual endeavors and will coordinate the overall NIDR effort. It is anticipated that new approaches to some of the behavioral aspects of dentistry will develop from the previously described workshop, the results of which will be available late in FY 1975.

Pain Research Centers. Efforts will continue to foster the development of oral-facial pain research centers to provide integrated loci of excellence for clinical and basic research. While the larger centers described earlier in this report are expected to support a broad panorama of activities including clinical teaching and research training, as well as research, the centers mentioned here are envisioned as smaller units devoted entirely to research achievement. Relatively few environments in this country now exist which have even the most rudimentary requirements for such centers. A beginning in this endeavor has been made at the University of Pennsylvania where a research project was initiated this year at a level of $67,000 to undertake a major clinical study of oral-facial pain and disturbed oral sensation. At the Dental Research Institute at the University of North Carolina, a multidisciplinary oral-facial pain center is being developed to focus on the pathogenesis of maxillofacial pain disorders and on new and more effective approaches to pain and anxiety control. Hopefully, the intramural setting of NIDR can also be utilized to develop a clinical pain research unit to complement its strong basic neurophysiology research effort. Among the types of research that could best be undertaken in these pain research centers are the following:

1. Studies of the etiology and pathophysiology of a variety of major oral-facial pain syndromes;

2. Development of better clinical methods for measuring the sensory and psychological components of pain and utilization of these methods in evaluating dental and oral-facial pain problems;

3. Comparative studies of the effectiveness and hazards of a variety of anesthetic agents used in dentistry.

Conference and Workshops. Planning sessions were held to prepare for two major workshop-conferences scheduled to be convened in the Fall of 1974. One will deal with the clinical diagnosis and treatment of oral-facial pain syndromes. Among the objectives of this conference are the following:

1. To develop improved terminology, standardization and classification for diagnosis and treatment evaluation

2. To establish the necessary physiological and psychological clinical observations for the study of oral-facial pain.

3. To develop a uniform method of recording and retrieving necessary data to facilitate comparative studies and to foster additional research.

The second workshop-conference will focus on the fear-anxiety syndrome that is such a major obstacle to dental treatment. Among the objectives of this conference are the following:

1. To review the current status of knowledge of anxiety in general and of dental anxiety in particular.

2. To identify more valid methods of quantitating anxiety.

3. To identify more reliable methods for the continuous physiological and psychological monitoring of patients' anxiety levels as a means of improving the evaluation of the efficacy of anti-anxiety treatment.

SUMMARY

NIDR has become identified as the key federal agency interested in pain research. During the past year NIDR contributed significantly to the revitalization of pain research by playing a leading role in developing conferences, workshops, and scientific meetings to discuss research opportunities in pain control and related behavioral sciences areas. For example, NIDR was instrumental in convening the International Symposium on Pain in Seattle, Washington, in May 1973, and gave strong support to the workshop-conference of the Section on Dentistry of The American Association for the Advancement of Science dealing with "The Control of Pain" at its annual meeting in San Francisco in 1974.

The impact of NIDR stimulatory activity has been to influence a number of high quality pain investigators to focus specifically on physiological and psychological pain research problems relevant to the oral-facial area. For example, a major study on acupuncture analgesia has been initiated with NIDR support at Massachusetts General Hospital. This study will evaluate the effectiveness of acupuncture in a number of experimental and dental pain situations. An important outcome of another study was the unequivocal documentation of cerebral electrical responses to tooth pulp stimulation. The cerebral tooth pulp-evoked potentials represent objective, quantifiable, non-verbal concomitants of central events associated with perception of pain. Further development of this important finding may provide a better method of investigating

acute pain in man than the subjective verbal reports by patients that investigators were forced to rely upon in previous studies.

The present report also contains a survey of all of the behavioral sciences program activities supported by NIDR. This survey represents an initial effort by the Pain Control and Behavioral Studies Program area to function as the overall coordinating and evaluating agent to provide a continuing overview in this field of emerging importance.

For the future, staff of the program will expand efforts to identify and involve quality investigators in pain research, and to increase the participation of Dental Research Institutes and Centers in pain and behavioral research. They will convene special meetings to evaluate the state of the art of pain and behavioral research, and will foster the development of oral facial pain research centers to assure maximum efficiency and high research productivity. Finally, they will evaluate and coordinate the various behavioral science components within NIDR, so that the Institute's programs in this area will become more cohesive and productive.

Drafted by A. Ganz

ANNUAL REPORT FY 74

DENTAL RESEARCH INSTITUTES AND CENTERS PROGRAM

The Dental Research Institutes and Centers Program is an experimental program which is completing its seventh year of operation. This program consists of five institutes and centers located within the Universities of Alabama, Michigan, North Carolina, Pennsylvania and Washington. The objective of institutes and centers is to expand and improve the quality of the scientific base which is essential for the development of measures to achieve optimum oral health. This objective is to be accomplished by pooling university resources and strengths with center funds to create an attractive environment which will entice nondental scientists to join dental investigators in their work on important oral health problems.

The institutes and centers are a part of the NIDR Extramural Program, and their research lies within the objectives of the six categorical program areas. Therefore, this report pertains to the more general and administrative matters regarding institutes and centers, leaving their research highlights to be described in the appropriate categorical program reports.

The five institutes and centers already named were funded at the beginning of the program and the same ones continue to be supported with no new institutes on the horizon at the present time. Annual appropriations for the program gradually rose from $3 million seven years ago to a peak of $6.5 million in FY 73 followed by a decline to the current $5.85 million level in FY 74. In order for the five institutes and centers to maintain their research activity during FY 74, it was necessary to transfer $1.3 million into the program, increasing its actual FY 74 budget to $7.15 million. However, even with this increase, the institutes and centers are still having financial difficulties. Since more than $4.1 million of the FY 74 funds were utilized for salaries plus fringe benefits, and an additional $1.9 million was required for indirect costs, only a relatively small amount was left for equipment, supplies, and other items needed for research. The effect of this situation has been to force individual investigators to seek research funds from other sources, usually through applications for independent project grants. While there is nothing intrinsically wrong with funding research by an individual grant within a center, nevertheless, the presence of many separately funded grants may tend to separate center scientists rather than to draw them together. If such a trend continued, it could eventually destroy the center concept and lead to collections of individual investigators, each going his own way without regard for what the others are doing. These potential dangers can be avoided by adequately increasing funds in future years. If funds are not increased it will surely be necessary to reduce personnel and projects, and the institutes and centers will no longer be able to maintain their viability as interdisciplinary, cohesive units.

In some institutes and centers, the past year has seen little change in regard to administration, personnel and program direction, whereas, in others, significant changes have taken place. The important developments which have taken place the past year in each institute are outlined below.

The Institute of Dental Research at the University of Alabama has had no major changes in personnel or research programs this year. Research emphasis continues to be directed toward periodontal disease and caries with a very strong program in connective tissue research.

In contrast, the Dental Research Institute at the University of Michigan has undergone a major reorganization under the leadership of its new Director, Dr. Harald Löe. The investigators at this institute have been grouped into three interdisciplinary teams to tackle three major problems areas of oral health: (1) periodontal disease and caries, (2) viral diseases of the oral cavity, (3) growth and function of the masticatory apparatus.

By necessity the Dental Research Center at the University of North Carolina has had to function this past year under the leadership of an Acting Director. Meanwhile its search committee continues to actively seek a new Director. It is anticipated that an appointment to this position will be made early in FY 75. During the current year the research at this center continued to emphasize growth and development but, in addition, a newly developed pain control program was expanded and strengthened.

The Center for Oral Health Research at the University of Pennsylvania has appointed a new Director, Dr. Howard M. Myers, who takes office on July 1, 1974. A favorable project site visit in January 1974 determined that the Center had made excellent progress since the last previous visit. Research continues to focus on periodontal disease and soft tissue studies.

The Center for Research in Oral Biology at the University of Washington is entering its last year of committed support. A renewal application for another five years of support has been submitted, and is presently undergoing comprehensive review. The review process which has already included a project site visit will be completed at the National Advisory Dental Research Council meeting in November 1974. The most pressing problem for this Center is space. Since it has no space of its own, it relies upon departments in which its affiliates have joint appointments to provide the necessary space. To solve this continuing problem, the Director of the Center is making plans to seek funds from private sources to construct a building for the Center. The research of this Center continues to focus on periodontal disease with related studies of salivary secretions and nutrition also being carried out.

Since the inception of the Institutes and Centers program there has been concern as to how each institute could make sure that high quality research would be practiced. To solve the problem of quality control of science, guidelines were developed whereby each institute or center would form a scientific review committee to evaluate the projects carried on within the center. According to the judgment of recent project visitors to the five institutes and centers, the overall problem of quality control is being dealt with effectively by the scientific review committees, and there is ample testimony to show that the quality of science has reached a high level. A number of young investigators, originally attracted to dental research by the institute environment, have recently achieved favorable recognition as established investigators in their respective disciplines as well as in oral health research; and students in increasing numbers are gaining valuable career experience in the laboratories of the institutes. While the impact of the scientific review committees on research quality has been undeniably good, there has been concern that in some instances a strong local review committee acting as a "Study Section," may also exert a negative effect on the progress in the center. It is believed by some that a powerful committee with its control over each and every research project may take away initiative and flexibility from the institute leader, so that his efforts to develop new and innovative programs may be hampered. If this dual mechanism of quality control of science is to function at an optimum level, it seems essential that the institutes must achieve a reasonable balance between the Director and the review committee.

The development of collaborative research has always been considered a key ingredient of productive center activity and the early years of center growth have seen a continuing increase in this kind of group research endeavor. Indeed, it can now be said that a number of important collaborative research projects have been developed between center scientists and other researchers not only at local and regional levels, but also at national and international levels. It has become clear, however, that relatively little of this activity has included interaction between institutes and dental schools. Therefore, efforts were made to stimulate interest on the part of dental schools. During the past year NIDR collected descriptive materials from each of the five centers and mailed copies to all of the dental institutions in the United States. The Center for Oral Health Research at the University of Pennsylvania announced a Visiting Scientist Program to interest faculty from other dental schools. The Dental Research Center at the University of North Carolina invited a representative from each of the southeastern dental schools to visit the Center and present a seminar to its investigators, and has begun periodic mailing of Center investigators' abstracts to schools throughout the country. The Center for Research in Oral Biology at the University of Washington distributes a regular newsletter covering Center activities, and is actively developing a collaborative project with dental faculty at the University of Oregon to conduct periodontal disease studies. The University of Michigan's Dental Research Institute also distributes a newsletter. All of these activities are intended to promote maximum utilization of the institutes and centers as

resources for dental institutions which do not have this type of support.

More than a year ago it was recognized that a true assessment of the total impact of the institutes and centers program would demand evaluation processes more comprehensive than the regular peer review. There was a need, it was felt, to develop a mechanism for evaluating the institute/center concept as an instrument of science policy. With that recognition an appropriate consultant was identified and a series of meetings was initiated. During the two meetings held in FY 73, the rudiments of an encompassing evaluation method began to emerge. This year more frequent meetings and increased staff and consultant effort have brought about accelerated progress towards the objectives of the project. The main objectives of the study are to answer three major questions: (1) Have the institutes/centers adhered to the guidelines set for them? (2) Have the institutes/centers achieved or are they achieving their original objectives? (3) Have the institutes/centers been more effective or less effective than other forms of support? In what ways? A detailed outline covering the areas of description, impact, economics, quality assessments, comparisons, hypothetical questions, and conclusions is nearing completion. According to the present schedule, the outline will be critically reviewed by consultants, finalized soon thereafter, and the evaluation itself will be initiated in FY 75.

Drafted by E. L. Rigg

PART IV

NATIONAL INSTITUTE OF DENTAL RESEARCH

ANNUAL REPORT

INTRAMURAL RESEARCH

July 1, 1973 - June 30, 1974

Compiled by

Dental Research Data Officer

National Institute of Dental Research

National Institutes of Health

Bethesda, Maryland

PREFACE

The NIDR Annual Report is intended to capture in printed form the essence of the Institute's total activities during the course of one fiscal year. The present format has evolved from our desire to make the Report more palatable to the reader, a better reference tool for its users, and less burdensome in preparation for its contributors.

A major change in compilation has been made in this issue to accommodate our several uses of the completed document. The Report for FY 1974 has been prepared in organizationally distinctive Parts to facilitate selective distribution to those who are concerned with or require as a working instrument less than the total publication. These are: Part I, Office of the Director, Research Projects and Indexes; Part II, National Caries Program; Part III, Extramural Programs; Part IV, Intramural Research; and Part V, Contracts.

For the third year, we have continued the practice of using a modified SSIE Notice of Research Project form (PHS 166) for the Individual Project Report. These are collected together as a section of Part I. This section, on blue paper, is accompanied by a number of indexes, for ease of retrieval and analysis, and a Classification Guide to Subjects and Categories.

We apologize in advance for any errors that may have escaped our attention and would appreciate your comments and suggestions so that we may continue to improve this document in the future.

Seymour J. Kreshover, D.D.S., M.D.
Director
NIDR

CONTENTS

PART I - OFFICE OF THE DIRECTOR

PART I - RESEARCH PROJECTS AND INDEXES

PART II - NATIONAL CARIES PROGRAM

PART III - EXTRAMURAL PROGRAMS

PART IV - INTRAMURAL RESEARCH PAGE

Director of Intramural Research - DIR 1

Environmental Mechanisms Section 3

Neural Mechanisms Section 7

Human Genetics Branch - HGB 13

Developmental Genetics Section 15

Population Genetics Section 21

Laboratory of Biochemistry - LBC 25

Cell Biology Section 27

Connective Tissue Section 35

Enzyme Chemistry Section 39

Protein Chemistry Section 45

Laboratory of Biological Structure - LBS 49

Experimental Morphology Section 51

Experimental Pharmacology Section 55

Molecular Structure Section 59

Structural Interactions Section 63

CONTENTS

PART IV - INTRAMURAL RESEARCH (Continued)	PAGE
Laboratory of Microbiology and Immunology - LMI	67
Microbial Physiology Section	69
Cellular Immunology Section	75
Clinical Immunology Section	81
Humoral Immunity Section	85
Laboratory of Oral Medicine - LOM	89
Neurobiology and Anesthesiology Branch - NAB	105
Clinical Investigations and Research Services Branch - CIB	107
Clinical Dental Services Section	109
Clinical Investigations Section	113
Oral and Pharyngeal Development Section	117
PART V - COLLABORATIVE RESEARCH PROJECTS	

Director of Intramural Research

Report of the Environmental Mechanisms Section
National Institute of Dental Research
Summary Report

Background

The Environmental Mechanisms Section has the mission of investigating the interactions among cells and the interactions of cells with their environment. Interest has grown in characterizing physiological and biochemical adaptations of specific cells to their particular ecological situation. Considering the basic mission of the NIDR, the area appropriate for study by this section is the relationship between bacteria and the oral cavity. Specific studies have taken three main directions, namely: 1) the investigation of the metabolism and growth of oral streptococci with sucrose as the dietary carbohydrate; 2) the mechanism of formation of extracellular dextran by these organisms; and 3) development of methodology for coding and interrogating data on phenotypic characteristics of oral microorganisms in a data bank.

The first area of concentration has been that of studying the environmental role of various simple sugars and complex carbohydrates in the growth processes of cariogenic streptococci, especially Streptococcus mutans. Such information should contribute directly to the development of a system for physically simulating the natural environment of such organisms namely, the mouth.

The second area of research is an extension of the study of cariogenic streptococci, but utilizes mutants which make aberrant extracellular polysaccharides. Since extracellular polysaccharides formation appears to be an integral part of the process by which pathogenic plaque deposits form, knowledge of the number of enzymatic steps involved in adhesive polymer formation would give insight into the number of points of possible prophylactic interdiction. That is, the more obligate steps involved, the more possibilities exist for blocking the formation of polysaccharide plaque.

The third area has been that of establishing a file of primary data on a large number of bacteria found in the oral cavity as well as related types. This file will provide a resource for asking both ecological and epidemiological questions of interest in dental research.

Progress This Year

Growth and Metabolism of Oral Bacteria

An important consideration in the impact of the micro-environment on these cocci is the study of the various enzymatic systems responsible for the initial attack on the sucrose molecule. Presumably, all the mechanisms have the cleavage of the glycosidic bond of the sucrose in common, irrespective of the nature of the products resulting from that cleavage. This study has isolated and characterized extracellular invertase as well as dextran sucrase and levan sucrase from the five serotypes of S. mutans, as well as from other oral streptococci. Further purification and characterization is in progress. Comparative studies are anticipated, especially with respect to determining

immunological simmilitude. Results so far suggest that S. mutans is a heterogeneous species; this fact warns against generalizations concerning the mechanism of carious lesion formation until more basic knowledge is available.

The products of sucrase activity (i.e., dextran and levan) are uncharacterized as well. An effort is now in progress to do structural determinations on the products of individual isolated sucrases. These studies may be extended to plaque polysaccharides, especially those presently uninvestigated, such as polysaccharides from actinomycetes.

Extracellular Polysaccharide Formation

Streptococcus mutans and sucrose have been implicated in the etiology of smooth surface caries. The formation of polysaccharide from sucrose by S. mutans is believed to be of major importance in this disease process. Both fructan and glucan type polysaccharides can be formed, but in the particular strain used in this study (SL-1), only glucan formation is important. This reaction is catalyzed by dextransucrase (glucosyltransferase). We have found several such activities in extracellular fluids by isoelectric focussing and electrophoresis in gels. The products made by these isolated enzymes are either water-soluble or insoluble. To understand the relationship between these enzymes and their relevance in caries etiology, a search for mutants deficient in these activities was initiated. Several mutants were isolated, but so far only one has been studied in detail. This 15-3 mutant forms much more water-soluble and less insoluble glucan than the parent. New enzyme assays were developed to quantify these observations. Also, the mutant adheres less to surfaces in the presence of sucrose. These results suggest that soluble glucan acts as a precursor for the insoluble glucan in the parent strain. In the mutant, this latter reaction appears to be blocked. Presently, we are investigating the chemical nature of the soluble and insoluble glucan polymers.

In depth studies of the ecological distribution and epidemiology of oral microorganisms require the handling of microbial strain data by large scale computers. Definition and standardization of the questions that are asked about microbial strains in a computer-compatible form is the first goal. Programs have been developed to enter data and retrieve it in a variety of ways for epidemiological, diagnostic, taxonomic, and ecological uses. The long term goal is to establish a world-wide data bank at a series of cooperating centers. Already agreeing to cooperate are the University of Queensland, Australia; the American Type Culture Collection, the Food and Drug Administration, United States; the National Collection of Type Cultures, England; and the World Federation of Culture Collections, International Association of Microbiological Societies.

Microbial Data Bank

A data file of primary data on a large number of bacteria found in the oral cavity and related types is being established. Already entered or in process are: Lactobacilli and streptococci from the American Type Culture Collection; Gram positive and Gram negative rods found in periodontitis and periodontosis

patients from Forsyth Dental Center; Streptococcus sanguis from Center for Disease Control; Streptococcus mutans from Ohio State University. Findings from analysis of some of these data have already demonstrated that new classification methods are needed for oral filimentous bacteria. The classical taxanomic codes do not apply. Further, computer comparisons of large volumes of data have allowed design of rational antibiotic therapy for periodontosis as well as design of selective diagnostic media. Reliable identification of bacteria which are potential or suspected etiological agents is vitally important to many studies of the epidemiology and ecology of oral diseases. One of the uses of this data bank will be used to define the characteristics which should be determined to give the most accurate identification.

Report of the Neural Mechanisms Section
National Institute of Dental Research
Summary Statement

During the last year the Neural Mechanisms Section has continued to focus its efforts on mechanisms of pain and temperature sensation.

The major objectives of the Section are to correlate structure and function in the trigeminal system with behavior related to pain perception and reaction. The trigeminal area is particularly well-suited for such studies because the central projection pathways are accessible for chronic electrophysiological recording techniques with minimal surgical intervention. In addition, earlier behavioral studies indicate that a lesion in human or monkey which interrupts connections between the rostral and caudal poles of the trigeminal brain stem nuclear complex, results in decreased facial sensibility to noxious and thermal stimuli. This procedure allows one to study neuronal events in the brain stem in trained animals under two distinct conditions: before and after sensory loss almost completely restricted to the detection and recognition of pain and temperature sensation.

Our approach in the last year has been multidisciplinary and includes the following research activities: (1) neurophysiological studies of the responses of trigeminal nerve fibers and brain stem neurons to noxious and innocuous thermal stimuli applied to the monkey's oral-facial area; (2) neurocytological studies of the organization of the trigeminal brain stem nuclear complex, with particular emphasis on those peripheral and central structures in the "pain" pathway; (3) correlative anatomical and physiological studies on the peripheral receptor types involved in oral-facial sensory function; (4) behavioral studies in monkeys trained to detect thermal stimuli and to escape from noxious thermal stimuli; and (5) psychophysical studies of pain and temperature "thresholds" in human.

Progress During the Last Year

Physiological Studies

Our approach to the study of pain mechanisms involves the use of noxious heat stimulation to determine the trigeminal peripheral and central neuronal populations which are capable of transmitting information about noxious stimuli. A contact thermal probe delivers precisely-controlled temperature stimuli in the range of 20 to 60°C. Step temperature changes of 10° per second are possible, permitting the investigator to deliver rapid, controlled noxious heat stimuli. Our present data indicate that three fiber populations respond initially to noxious thermal stimuli (greater than 45°C) applied to the monkey's face: warm fibers, and myelinated and unmyelinated heat nociceptive fibers. Warm fibers whose firing rates were increased during warming and suppressed during cooling, often responded to temperatures above 45°C. The response profiles to noxious heat displayed higher frequency initial transients than those to warming, although firing rates were reduced or suppressed completely after 2-3 sec of stimulation. Maximum firing rates to stimuli in the noxious heat range were dependent on the final temperature

reached and independent of adapting temperature (in the 30^{o} to 37^{o} range) and rate of change of the temperature shift. Repeated noxious thermal stimuli suppressed the response to innocuous warming stimuli although responses to stimuli above 45^{o}C were not changed. Warm fibers had single spot receptive fields (300 um in diameter) and conduction velocities in the A delta and C fiber range. Heat nociceptors with conduction velocities in the A delta range had receptive fields of 1-2 mm diameter and had threshold responses to constant temperatures and rapid temperature shifts at 35^{o}C (warm fiber thresholds were usually less than 30^{o}C). They also differed from warm fibers in that the responses to noxious heat improved with repeated stimulation (sensitization). Heat nociceptors with conduction velocities in the C fiber range had thresholds above 40^{o}C and responded weakly to final temperatures below 48 to 50^{o}C. They also sensitized to repeated stimulation near threshold. Repeated stimulation above 50^{o}C, however, suppressed their response.

Two other fiber populations were studied which responded to noxious heat after repeated stimulation. Cold fibers with conduction velocities in the A delta range had firing rates which increased during cooling and were suppressed during warming. They often responded initially to thermal stimuli above 55^{o}C; repeated noxious heat stimulation sensitized these fibers and lowered their thresholds to below 50^{o}C. High-threshold mechanoreceptors, responsive to pinprick stimulation, had conduction velocities in the A delta range, and responded to thermal stimuli above 50^{o}C after repeated stimulation. Many larger A beta fibers exhibited low threshold, slowly-adapting responses to single hair movement which were suppressed by temperatures above 45^{o}C. In summary, noxious heat stimulation increased the activity of most small myelinated (A delta fibers) and unmyelinated (C fibers) afferent fibers innervating the oral-facial area of the monkey. The activity of many larger myelinated (A beta fibers) fibers was suppressed. These reciprocal events may play an important role in the recognition of pain sensation produced by noxious heat stimulation.

To what part of the trigeminal brain-stem nuclear complex do the above small fiber populations responsive to noxious heat stimulation project? How do these responses compare with those of the incoming fibers? Our preliminary data in anesthetized monkeys suggests that noxious heat activates neurons located primarily in the caudal part of the trigeminal brain-stem nuclear complex and that peripheral fiber responses to low-threshold mechanical stimuli, innocuous thermal stimuli, and noxious input converge on the same neurons.

Anatomical Studies

The older neurology and neurosurgery literature contains several pieces of evidence which implicate the lower end of the spinal trigeminal nucleus (nucleus caudalis) as an essential site for the perception of facial pain. This location is the only site in the trigeminal brain stem nuclei where second order neurons can be found which respond exclusively to painful facial stimuli.

During this past year, our electron microscope studies have further implicated nucleus caudalis as an important site in the trigeminal pain pathway. The

V nerve endings in the substantia gelatinosa layer (SG) of nucleus caudalis differ morphologically from the V nerve endings in all other parts of the trigeminal brain stem nuclei. In the SG layer, V nerve endings are long and thin, have a scalloped outline, and have a dark axoplasm. V nerve endings elsewhere are rounded, bulbous structures with pale axoplasm. The primary trigeminal neurons in the trigeminal ganglion are easily divided into pale neurons which include the largest neurons with large caliber axons and dark neurons which include the smallest neurons with either small myelinated or unmyelinated axons. It is precisely these small caliber axons which physiological studies in our Section have implicated in the transmission of pain and temperature sensation into central nervous system. These anatomical studies suggest that the dark V nerve endings, found exclusively in the SG layer, originate from the small dark primary trigeminal neurons.

The V nerve endings in the SG layer of nucleus caudalis are surrounded by dendritic spines, dendritic shafts and small axonal endings. These processes are linked together synaptically in structures called glomeruli. In each glomerulus a V nerve ending forms asymmetrical axodendritic synapses on two kinds of dendritic spines and on dendritic shafts. These dendritic processes in turn are linked by two kinds of dendrodendritic synapses. The V nerve endings receive symmetrical axoaxonic synapses from axons of intrinsic neurons.

These observations show that at least two morphologically distinct neuronal cell types send their dendrites into the SG glomeruli. We have devoted considerable effort to developing Golgi techniques for adult animals that would permit us to determine precisely how many neuronal cell types contribute to the neuropil of the SG layer. The results of these Golgi studies have shown that the SG layer contains three distinct neuronal cell types which can be distinguished by their dendritic branching pattern, distribution of dendritic spines, axonal branching pattern, and the intralaminar and extralaminar distribution of their dendrites and axons. The neurons of the SG layer include (1) Islet cells-neurons whose axonal and dendritic arbors are confined to the SG layer, (2) Stalked cells-neurons whose dendrites and axon traverse the SG and marginal layers, and (3) Spiny cells-neurons whose dendrites and axons pervade all three layers of nucleus caudalis. In addition, neurons in the marginal and magnocellular layers send their dendrites into the SG layer.

The Golgi studies suggest that contrary to earlier anatomical and physiological concepts, the SG layer is composed of three morphologically distinct neurons. One of these, the islet cell, satisfies all of the anatomical criteria for an interneuron whereas the others are involved in integration of synaptic activity between the three layers of nucleus caudalis.

Correlative anatomical and physiological studies have been concerned with the morphology of receptors associated with stiff hairs on the monkey's face that respond to weak mechanical stimuli. Slowly-adapting (SA) responses recorded from dissected strands of the infraorbital nerve were histologically-verified to be associated with sinus and non-sinus hairs found above the lip. Two types of SA responses could be distinguished on the basis of spontaneous activity, regular or irregular discharge patterns, and the presence

or absence of maintained activity for more than 90 sec to mechanical displacement of the hair or adjacent skin. Rapidly-adapting units also were found associated with these stiff hairs above the lip. They exhibited "on" and "off" responses only during movement of the hair. Light and electron-microscopic studies of receptors associated with sinus hairs have revealed three distinct types of endings: (1) Merkel-cell neurite complexes, (2) lanceolate endings and (3) a new structure which has characteristics similar to Ruffini and Golgi tendon organ endings found in other areas of skin. The Merkel-cell neurite complex and the lanceolate endings are found in the upper half of the hair follicle. Below the middle of the hair, the hyaline membrane thickens with a zone of compact longitudinal collagen fibries forming beneath it. In this zone of compact collagen, axonal endings filled with mitochondria are seen and intertwine with and surround the collagen fibrils. These endings are invested by a single Schwann cell though there are bare zones directly contacting collagen fibrils. A similar type of ending has been found in the hair follicle of non-sinus hairs associated with slowly-adapting mechanosensitive fibers. It appears from the present data and previous reports of similar receptors in non-facial skin, that the slowly-adapting responses are associated with the Merkel-cell neurite complexes and the "new" ending, and that the lanceolate endings are the terminals of the rapidly-adapting mechanosensitive fibers.

Behavioral Studies

In these experiments we are developing a model for the study of peripheral and central nervous system mechanisms of the sensory-discriminative and motivational-affective components of pain perception and reaction. Rhesus monkeys or humans are trained to detect innocuous warming and cooling stimuli and to escape noxious thermal stimuli. A thermode, similar to one used in the physiological experiments described above, is positioned on the face and warming and cooling stimuli are applied. Each subject is trained to depress a panel-switch on each trial until the relevant stimulus change is detected. The subject must release the switch within a predetermined period of time after the stimulus change to be rewarded by liquid (juice or water) in monkeys or by knowledge of a correct response in humans. The behavioral measurement of sensory performance is determined by the subject's reaction time (RT), measured as the time interval from the beginning of the stimulus change to the release of the switch. In one paradigm, depression of the switch produces an increase in temperature and the subject must detect the termination of the stimulus (cooling). On some trials, however, the temperature shifts reach the noxious heat range (45^{o} - 51^{o}C) and the subject may terminate and escape the stimulus by releasing the switch early. No reward is given if the subject releases early. Under these conditions, the escape threshold for water-satiated monkeys is approximately 47-48^{o}C. At final temperatures of 48^{o}C or higher, the probability of an early release is greater than 0.5 and latencies are less than 3.0 sec. These escape thresholds are independent of the adapting temperature (range of 30-37^{o}C) of the skin. Lip movements associated with noxious heat stimuli have been monitored and concordant with the behavioral results, they occur only at temperatures of 48^{o}C or higher. Behavioral escape thresholds, however, are dependent on the motivational state of the subject. Water-deprived monkeys exhibit escape thresholds greater than 51 to 53^{o}C.

In a similar behavioral paradigm, humans exhibited thresholds for pricking pain of approximately 47-48°C, coinciding with the results obtained with water-satiated monkeys.

Detection thresholds to warming stimuli have been examined in another paradigm. For warming stimuli greater than 1°, RT's are determined solely by the rate of stimulus change, and thus independent of the size of the temperature shift. This result occurs at all adapting temperatures between 25 and 40°C, although the RT's are negatively correlated with adapting temperature. In addition, for interstimulus intervals less than 20 sec, RT's to the second stimulus are suppressed by initial stimuli of large magnitude (greater than or equal to 3°). These findings indicate that RTs vary with changes in stimulus parameters. Sensory detection thresholds, as reported by others, show similar changes when stimulus parameters such as adapting temperature and interstimulus interval are varied. It appears that reaction times are a good behavioral measure of sensory performance.

Future Plans

One of our aims is to correlate central nervous system neuronal activity in the trigeminal system with behavioral performance in awake rhesus monkeys trained to escape noxious thermal stimuli applied to the face. Are there neurons which respond exclusively to noxious stimuli? Are there neurons whose activity is correlated with escape responses to noxious stimuli and not with motor responses to innocuous stimuli? Does the motivational state of the monkey alter the activity of neurons responsive to noxious heat stimulation? There are the kinds of questions we hope to answer in these projected studies.

Other studies will be concerned with correlating structure in the trigeminal brain-stem nuclear complex with the functional properties of neurons responsive to innocuous and noxious thermal stimuli. The role of the substantia gelatinosa layer in oral-facial pain mechanisms and its interrelationships with other layers of nucleus caudalis will be studied. Golgi and electron-microscopic studies will attempt to further identify the neuronal cell types of the marginal and magnocellular layers of nucleus caudalis to the elaborate on the interlaminar synaptic connections.

Summary Report of the Human Genetics Branch
National Institute of Dental Research

Congenital malformation in general, and craniofacial anomalies, in particular, continue to be major program areas of the Human Genetics Branch. During the past year the activities of the Branch have been devoted almost exclusively to these areas.

The Developmental Genetics Section is concerned with etiology and pathogenesis of craniofacial malformations in experimental animals. Emphasis is in two areas: 1) basic studies in facial embryology utilizing interspecies grafting techniques; and 2) studies of environmental factors contributing to the production of congenital anomalies in genetically susceptible strains of animals. Using strains of animals which develop facial defects spontaneously either because of single gene mutation or polygenic predisposition, studies are directed at defining the developmental basis of these defects and at modifying environmental factors in order to alter the expression of the genes. The aim of these studies is to develop models of genome-environment interaction which may ultimately lead to practical preventive measures in humans.

The Population Genetics Section conducts studies on human families and populations with the aim of better elucidating genetic mechanisms in craniofacial anomalies, and of identifying agents in the maternal and/or fetal environment which also contribute to the formation of defects. Human studies are designed to produce leads which can be further elaborated and refined through animal studies. As more definitive models are developed through laboratory experimentation the results are examined and tested, in the field, for relevance to the human situation.

Further studies relating to the relationship between epilepsy and cleft lip and palate show that the frequency of epilepsy among mothers of cleft lip patients is approximately five times that in the general population. Although the evidence is not entirely conclusive, it appears that the increased risk relates to defects of the primary palate and not the secondary palate, i.e., cleft lip with or without cleft palate rather than isolated cleft palate. It has generally been assumed, but not satisfactorily demonstrated, that this increased risk related to epilepsy is due to the anticonvulsant medication.

We have found that diphenylhydantoin administered to A strain mice produces both cleft lip and cleft palate. There is some evidence that these clefts in mice are produced secondarily from hemorrhage into the areas of fusion. Such a mechanism could also be operative in the human situation and might be tested by angiography in infants with cleft lips born to epileptic mothers.

Another promising area of investigation relates to studies of x-irradiation of A/Jax mice. It has been found that an extremely high frequency of cleft lip can be produced on day 8 of gestation with 100R radiation. However, a similar dose of radiation on day 10 of gestation results in complete absence of clefts. Histologic examination of embryos irradiated on day 10 shows localized cell death in the floor of the forebrain with marked reduction in the size of the forebrain. No other effects are identifiable. We hypothesize that this selective cell death and reduction in brain size results in a relatively greater mass of prospective

lip tissue and hence enhances the fusion process. These findings suggest one pathogenetic mechanism which may have wider significance in the etiology of cleft lip and palate. This interpretation and speculation is supported by our studies of facial morphology in parents of children with clefts of the lip.

Summary Report of the Developmental Genetics Section
Human Genetics Branch
National Institute of Dental Research

The major focus of the Developmental Genetics Section is on the control of normal and abnormal development of the face. Embryological studies are concerned with the processes by which the head and face develop. Mutant and highly inbred strains of mice with CLP or CP or predisposition to these traits are examined for differences from normal animals during morphogenesis and for their responses to teratogenic and other stimuli.

Embryology

During the past year activity related to cell tracing studies consisted mostly of preparing the results for publication. Results of experiments related to the mechanism of neural crest cell migration (in chick embryos) and to normal formation and clefting of the primary palate (in the mouse) are presented below.

Neural Crest Cell Migration. Studies on the nature of the environment through which crest cells migrate were conducted in collaboration with R. M. Pratt. Further evidence for the presence of hyaluronate in the subectodermal cell-free space through which the cells migrate was provided by a combination of radioautography and DEAE Cephadex column chromatography. Labeling in this space disappears if cetylpyridinium chloride (CPC- a precipitant for mucopolysaccharides) is omitted from aldehyde fixatives used for radioautography. That hyaluronate is the only mucopolysaccharide extracted by the fixative has been shown by subsequent chromatography of fixative after completion of the fixation procedure.

Label is found in the subectodermal space after CPC-aldehyde fixation and persists as a patchy layer in the basement membrane region in material fixed without CPC. The distribution of label correlates reasonably well with the appearance of filamentous material demonstrated by scanning and transmission EM (see below).

Scanning EM Studies (conducted in collaboration with A. J. Steffek). Just prior to neural crest cell migration a filamentous meshwork appears in the region of the subectodermal basement membrane. Much more sparsely distributed filaments also appear in other areas of the subectodermal space. Re-examination of previously obtained transmission EM's confirmed the observations. The presence of labeling following administration of proline-H^3 suggests that the filamentous material may contain a form of collagen.

The three-dimensional morphology of migrating crest cells has now been characterized by scanning EM. Unlike mesodermal cells, which have extremely long processes (0.1-0.2 μ in diameter) and a polygonal shape at this stage of development, the crest cells have only short "microspikes" and a very characteristic "bottle" shape with major process at the leading edge. This configuration is rather similar to that of fibroblasts migrating

in a collagen gel.[1] The crest cells are highly oriented and there is little evidence of extensive contact between the cells and their surroundings.

Cell culture studies (with J. Gaare and R. M. Pratt). These studies have been initiated to examine the behavior of migrating crest cells in experimentally altered environments. Cranial crest cells only gradually (over 24 hours or more) become adhesive to the substratum. Collagen gels are now being constructed to test the behavior of crest cells in a three-dimensional matrix in vitro.

Neural Crest Conference. This 3-day (August 27-29) conference was co-sponsored by the Fogarty Center. Some 60-70 scientists from five countries discussed the normal and abnormal development of the neural crest. A summary of the proceedings of the conference was published in the January, 1974, issue of Developmental Biology.

Normal Development and Clefting of the Primary Palate

Inbred strains. The A/J strain of mouse and its related strain CL/FR are the two inbred strains which have cleft lip and palate at a frequency over 1%. A/J has 12-15% and CL/FR 18-20% cleft lip in newborns. Both are under study in this laboratory. Genetic analysis has shown that the pattern of inheritance in A/J is similar to that most commonly suggested for man.[2] The morphology and development of the malformation in the mouse are also similar to much of human cleft lip and palate. We have carried out several experiments on these strains to see whether environmental factors can modify the frequency of expressed cleft palate. X-irradiation, the drug diphenylhydantoin (Dilantin(R)), which has been implicated as a cause of human cleft lip,[3] and thyroid hormone are the agents being used.

Studies were continued on the interacting radiation and genetic susceptibility for CL(P) in A/J strain. In a dose-response study on day 8 of gestation, the relationships between lethality and malformation among the surviving embryos are compatible with the two-threshold concept of a continuous spectrum of liability, in which a small insult malforms, while a more severe one kills the embryo. Histological studies indicate that cell death is most pronounced in the neural plate, an observation consistent with the fact that subsequent malformations are usually limited to neural plate derivatives: the forebrain, eye and facial mesenchyme.

Recent additional studies have led to a change in the interpretation of a previous observation, namely that 100R radiation on day 10 caused the "disappearance" of CL/P in embryos examined on day 17. This observation had been interpreted as selective lethality for embryos that were already weak. Earlier examination of litters following day 10 radiation showed that there was insufficient embryo death prior to lip formation to account for the absence of cleft lip embryos. Detailed histological analyses of embryos after radiation indicate that localized cell death in the floor of the forebrain between the optic stalks is responsible for a severe reduction in the size of the forebrain as compared to that which

would normally be observed at the time of lip development. There is very little cell death in the facial mesenchyme and the fronto-nasal processes of either the control or the radiated embryos. It now appears that the reduction in brain size results in the medial and lateral nasal processes being closer together, so enhancing the fusion process, and reducing the numbers of affected individuals. These results suggest that the proportions of the brain and facial mesenchyme are of critical importance for normal development of the lip and palate.

Diphenylhydantoin (DPH), an antiepileptic widely used in man, has been associated with an increased risk of cleft lip in humans.[3] It can induce enzymes, change calcium uptake and modify hormone responses. In large acute doses it has been demonstrated to produce cleft palate in mice.[4] We wished to test its relation to cleft lip in lower and chronic doses more related to the human experience. Two mouse strains which had similar susceptibility to cleft palate but differed in cleft lip were tested. CL/FR has 18-20% CLP while Star does not have CLP. In the CL/FR strain, DPH injected daily the first fifteen days of pregnancy in doses about twice that used to treat humans produced both cleft lip and cleft palate and also produced a type of lip hematoma not previously observed. In Star mice a dose twice as large as for CL/FR did not produce cleft lip, cleft lip and palate or isolated cleft palate.

Star females tolerated doses which killed all CL/FR females. Steroid levels in the two strains did not differ significantly from controls, so it appears that the DPH teratogenecity does not act through a steroid mechanism. The CL/FR strain has been shown to have inducible aromatic hydrocarbon hydroxylase liver enzymes while the Star mice are not inducible as tested by Dr. Danial Nebert, Developmental Pharmacology Section, NICHD. These strain differences will allow further study of the genetics of the response to diphenylhydantoin.

Observations of cyanosis among the cleft lip newborns of A/J strain have been made by Fraser and associates at McGill, as well as in this laboratory. A similar phenomenon occurs in the CL/FR strain. During the last year this cyanosis has been studied in the CL/FR strain and appears to have two bases. Many of the abnormal mice can be stimulated to become acyanotic by pinching or handling. These observations suggest that the circulatory problem in such animals arises from either some central nervous system defect or dehydration, due to lack of nursing. In individuals with more severe clefts, usually bilateral CLP, cyanosis is associated with anatomic defects of the heart. Dissection has revealed both intra-atrial septal defects and patent ductus arteriosus, both of which occur in grades of morphological severity, and appear to share a common pathogenesis. Preliminary embryological studies from Dr. Fraser's group, and studies in progress here suggest that the development of the heart and lip are correlated.

Thyroid hormone is a well recognized stimulant of oxidative metabolism. Further, it possesses a powerful capacity for induction of enzymes in

mammalian embryos and fetuses, as well as for modulating the action of other hormones as inducers of enzyme activity. Accordingly, it might be expected that altered levels of thyroid hormone would modify mammalian development, just as it does so remarkably in amphibians.

Injection of thyroid hormone during pregnancy has been reported to reduce spontaneous cleft lip in the Strong A strain of mice,[5] which is closely related to A/J and CL/FR. However, others have reported lack of effect on A/J mice. We have recently completed a large study of the effect of injected thyroid hormone, and conclude that it reduces the risk of cleft lip in A/J mice. This effect, however, only slightly exceeds that obtained by the injection of the vehicle alone. Experimental manipulation of the A/J mother on day 9 and 10 of gestation, whether involving thyroid hormone or not, thus appears sufficient to selectively kill the embryos that are prone to have defects, and are presumably already debilitated or retarded at this stage of development.

During the year we have continued our study of the oel gene which produces isolated cleft palate with open eyelids at birth. We have demonstrated a new trait, abnormality of the cornea, which identifies the previously unrecognizable heterozygote for this gene. The biochemistry of the defect in the heterozygote is being investigated in collaboration with Dr. Bergsma and Dr. Varma of the NEI. Genetic studies of the relation of oel stock to the T (tailless) genes have demonstrated that oel stock has genes that supress the developmental abnormality of the spinal column usually produced by the T gene in 70% of F_1 animals. The nature of the interaction of these genes, whether by early lethality, or by compensating for the action of the T gene to allow normal development, is under continuing investigation.

One of the problems for investigators of the embryology of genetic defects of palate development is the identification of the embryo which will have CP before palate closure. During the year we have established a new stock, pink eye eleven, which has unpigmented retina and cleft palate in the homozygote. This combination has the advantage that the retina normally develops pigment on day 11 of gestation so the presumptive defective palate shelves can be positively identified for experimental study well before palate closure on day 15.

The Twirler genotype is identifiable in the heterozygote (Tw/+) by a vestibular abnormality that results in a charcteristic behavior. In the homozygote (Tw/Tw) there occur a spectrum of facial deformities ranging from severe mid-face cleft through bilateral and unilateral cleft lip and palate to isolated cleft palate. About half the Tw/Tw animals have CP and the rest have more severe defects. The primary facial dysplasia in this genotype appears to involve aberrant development of the median nasal processes, as contrasted to the reduction in the bulk of the palatal shelves seen in other types of CP. In Tw/Tw animals with CP there is a scar in the lip, suggesting that the primary palate closed abnormally. There are associated defects around the incisive foramen as well as secondary palatal clefts.

One of the major chromosomal disturbances in man possessing a clear association with facial clefting in man is trisomy. Within the last year, Dr. Beverly White, LEP, NIAMDD, has produced experimental trisomy of chromosome 19 in the mouse.[6] Substantial numbers (> 20%) of these trisomic mice demonstrate isolated cleft palate. In collaboration with Dr. White we are now breeding the trisomic animals and find that in addition to CP, they have a small retruded mandible and small tongue. Since their body size is reduced about 30% at birth, and there appear to be particular genotypes associated with the CP, it may be that the generalized growth retardation acts to "uncover" the action of genes which would not otherwise produce the defect. Breeding experiments can test this idea.

Future Plans

The research program of the section will be carried on in the context of the new Laboratory of Developmental Biology and Anomalies. Proposed new projects or extensions of existing projects include the following.

1. The mechanisms by which the normal neural crest cells migrate and the significance of the newly discovered fibrillar meshwork for this migration will be the subject of several collaborative studies in chick embryo.

2. Experimental modification of the production of matrix; and the synthesis of the fibrillar network in order to test its importance for cell migration are planned.

3. Migrating neural crest cells appear to be particularly susceptible to hypervitaminosis A. This agent will be systematically examined in the neural crest tissues of normal and predisposed mice both in vivo and in vitro.

4. The proliferation kinetics of cells in lip and palate of strains of mice with spontaneous clefts will be compared to controls, both with and without antimetabolites and specific anti-mitotic agents.

5. In collaboration with Dr. Danial Nebert, NICHD, the action of diphenylhydantoin in the production of cleft lip will be studied in the context of differences in enzyme induction between susceptible and resistant strains. Concurrently, a detailed embryological examination of the processes leading to clefts in the treated animals will also be undertaken. Efforts to remove treatment artifacts due to injection stress will be made by incorporating the diphenylhydantoin in the diet. An analogous study will be done on the effects of thyroid hormone incorporated into diet rather than given by injection.

6. In corollary fashion, more general exploration of maternal stress in relation to cleft lip production will be initiated, in concert with continuing studies of maternal stress in relation to cleft palate.[7]

7. Mouse mutants will be utilized as donors for *in vitro* studies of the palatal shelves of abnormal embryos and their normal littermates. Further efforts will be made to characterize mutant-specific defects in early stages of development which should allow identification of embryos at high risk before the time of palate or lip closure.

8. Studies of the interaction between the genes producing different defects of midline structures will be continued. Genetic and morphologic analysis of the CP that is associated with trisomy will be continued in collaboration with Dr. White, LEP, NIAMDD.

9. Further studies of the specific defect in the *oel* mice which results in the characteristic facial stigmata described above will be undertaken by both histological and biochemical techniques.

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Summary Report of the Population Genetics Section
Human Genetics Branch
National Institute of Dental Research

The Population Genetics Section was established to study genetic variation in human populations with concentration on those genetic variants associated with disease states. During the past year the focus of the section has been primarily on the study of congenital malformations, particularly cleft lip (CL) and palate (CP); utilizing both family and population data. Major areas of study include (1) characteristics of families with oral clefts, (2) maternal factors in congenital malformation, (3) congenital malformation in the American Indians as a defined genetic isolate, and (4) genetic studies of oral diseases, anomalies and development.

Progress

Studies on facial morphology in relatives of oral cleft patients are being conducted in collaboration with the Lancaster Cleft Palate Clinic, Lancaster, Pa., and the Department of Orthodontics at the University of Michigan, Ann Arbor, Michigan. The objectives of these studies are to utilize parameters of facial morphology in an attempt to define different subgroups of cleft families and to determine if facial measurements can be useful for genetic counseling. In addition, if certain aspects of facial morphology can be shown to be predisposing to the production of oral clefts, this information may be useful in better understanding the pathogenesis of the defects. Data from frontal and lateral cephalograms have been collected from a sample consisting of 223 parents of children with cleft lip with or without cleft palate, 124 parents of children with isolated cleft palate and two control groups of parents. Of the latter, one group consists of 115 individuals from Lancaster, Pennsylvania, and the other of 132 parents of normal children from Ann Arbor, Michigan. All parents of cleft children were obtained from Lancaster.

The most definitive findings are observed in the cleft lip with or without palate group. The parents of these children show small, but a statistically significant increase in interorbital distance, as well as a significant decrease in upper face height. These changes result secondarily in increased mandibular prognathism and a somewhat concave facial profile. Although these changes occur in both sexes, they are greatest among the fathers.

These findings are consistent with the hypothesis that a relative deficiency of embryonic facial mesenchyme may play a role in the production of cleft lip, with or without cleft palate. In our analyses, we were unable to demonstrate directly that the observed changes reflected genetic predisposition of the parents. Whatever the cause, we concluded that changes in facial morphology are too small to be of practical use for risk estimation during genetic counseling.

In order to determine the maximum sub-threshold manifestations that may occur in (designated "normal") relatives of oral cleft patients;

analyses of 30 pairs of monozygous twins discordant for CLP are being pursued. Each of the 30 unaffected twins has a genetic constitution identical to his affected twin sibling and theoretically has shared a very similar pre- and postnatal environment. This group therefore is expected to show the most extreme deviations in facial morphology to be found in relatives of oral cleft patients. Age and sex matched control groups of 8-10 individuals has been obtained for each of the 30 twins.

A population study attempting to demonstrate the presence of maternal effects is nearing conclusion. In collaboration with several investigators in human genetics, more than 5,000 pedigrees of oral cleft families have been reviewed. All pedigrees with half sibs of the cleft proband have been identified and tabulated. Approximately 500 half sibships have been obtained thus far, with no evidence of greater risk of recurrence among maternal than among paternal half sibs. These findings suggest that maternal factors persistent from one pregnancy to the next (e.g., genetic metabolic errors or deficiencies) do not play a major role in the genesis of oral clefts.

Studies involving demographic parameters related to birth weight from available records on the American Indians have shown a highly significant association between prenatal care and death of the newborn. Thus, women who receive no prenatal care showed approximately a 40% increase in mortality among their newborn infants and about a 4% decrease in birth weight.[1] These effects persisted even after correction for genetic and environmental co-variables. The possibility remains however that other factors are responsible for these effects, rather than prenatal care *per se*.

Since variability in human birth weight has been demonstrated to be correlated highly with such attributes as intelligence and growth,[2] factors which influence variation in human birth weight are important to identify and quantitate. Previous twin and family studies[3] have shown a significant genetic influence on birth weight. Furthermore the greater positive correlation between birth weight of maternal than paternal first cousins has been purported as constituting evidence for a significant maternal effect. By examining 84 offspring of monozygous (MZ) twins, we have demonstrated that the variance of sibship means in male MZ half sibships is four times as great ($p = .025$) as the variance for female half sibships (derived from genetically identical mothers). These findings are evidence for the existence of a genetically determined maternal effect on human birth weight.

Because of the prevalence of intertribal marriages among the American Indians, a unique opportunity is provided to seek further confirmatory evidence regarding genetically determined maternal effects. Mean birth weights have been calculated for the largest 12 tribal groups composed exclusively of intertribal matings. Preliminary results comparing birth weights from matings involving intertribal marriages show significantly less variation from the mean birth weight of the mother's original tribe

than that of the father's. Additional studies are now underway to explore possible interaction with admixture and other important confounding variables before these results can be considered conclusive.

Although the overall incidence of congenital malformations does not vary greatly among different racial groups, enormous differences with respect to specific malformations have been reported. Of these, one of the most striking is the skeletal malformation, polydactyly.

A thirteen-fold difference in postaxial type B polydactyly has been reported for Negroes and Caucasians.[4] To characterize the factors involved and, if possible, to discover the cause of these racial differences, be they genetic or environmental, is important for the understanding of the pathogenesis of any malformation. We have recently completed and are in the process of submitting for publication a study of polydactyly in the American Indian.[5] Significant findings from this study include an overall incidence of 2.40 per thousand live births which is twice the estimated frequency in Caucasians. Preaxial type I polydactyly was found to have an incidence three to four times reported estimates for Caucasian or Negroes. Since this malformation has been induced by the teratogenic drug, Thalidomide, the possibility of an environmental teratogen operating uniquely among the Indians was considered. There is, however, no direct evidence to support such an hypothesis. Incidence estimates for different degrees of admixture support an additive genetic hypothesis.

Future Plans

The simultaneous occurrence of facial clefting with other major and minor congenital anomalies is well known. A striking association between cleft lip with cleft palate and a specific heart malformation, i.e. atrial septal defect of the secundum type, has been observed in experimental strains of mice.[6] Moreover, Shah et al.[7] have reported finding atrial septal defects among congenital heart disease in 20% of children with both CL(P) and CP who died early in life. Another report[8] of a high frequency (0.2) of minor electrocardiographic anomalies in a CL(P) patient population has prompted us to design and execute a study utilizing the patient population of the Lancaster Cleft Palate Clinic: (1) to deliniate specific types of facial clefts which may be associated with congenital heart defects, (2) to estimate the incidence of congenital heart disease in an ambulatory cleft lip and palate clinic population, and (3) to define and explain minor ECG anomalies in this population. Presently, data pertaining to these points are being collected.

The association between maternal epilepsy and CL(P) has now been documented in a number of populations including the U.S. Air Force.[9] Although the basis for this association is not yet clear it represents the best presently recognized situation with real potential for prevention of at least a portion of oral clefts. A study is now being initiated in collaboration with the Lancaster Cleft Palate Clinic to determine more

precisely the type of clefts involved, factors in the family history which affect the risk, and the portion of cleft patients in a clinic population whose cleft defect can be related to maternal epilepsy.

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Laboratory of Biochemistry
Summary Report

The four sections in the Laboratory have continued to maintain active programs in several fundamental areas of biochemistry. They are making important contributions to the pool of basic knowledge necessary for the prevention and cure of disease, particularly oral disease.

The Protein Chemistry Section has continued its efforts in the study of collagen chemistry. As more details of the chemistry of this molecule become known, applications to molecular structure, collagen fibril structure and collagen interactions with other connective tissue components become possible. To further these applications, the Chief of the Section spent the 1973-74 year at Oxford University learning and utilizing electron microscopy and biophysical techniques. A particularly important contribution that arose from the work done at Oxford was the demonstration that collagen fibrils have a substructure, the microfibril, which consists of a regular helix of collagen molecules. Future plans of the Section depend on the combined application of chemical, ultrastructural and biophysical methods to connective tissue structure. Organizational changes within NIDR (see below) will facilitate these plans by encouraging collaborative efforts between the Laboratory of Biological Structure and the Protein Chemistry Section.

The Connective Tissue Section continues its work on procollagen, the biosynthetic precursor of collagen, and on hereditary diseases of connective tissue. Both topics are highly competitive research areas which were opened in large part due to the efforts of the group. The Section continues to be one of the world's leading research groups in connective tissue biosynthesis. This is evidenced by the large number of guest workers that enter the program to learn the biochemical methods used in the study of connective tissue disease. They have now identified the molecular defect for several hereditary collagen diseases in man and animals. These results are important in clarifying the significance of several biosynthetic steps.

The Enzyme Chemistry Section has for some years been the leader in the study of transglutaminase, the enzyme that makes γ-glutamyl-ε-aminolysine crosslinks in fibrin and other proteins. The number of other proteins with this crosslink continues to increase, demonstrating its very significant biological role. The enzyme can also be used as a probe of protein structure and to introduce artificial crosslinks into proteins in a specific manner. These studies provide a good example of how basic research initially undertaken simply as an interesting problem often shows a biological relevance as studies progress. Future plans emphasize this biological aspect.

The Cell Biology Section has as its general problem area the investigation of cellular events that regulate growth and differentiation. Evidence for a ribosomal protein whose synthesis is limiting in certain

growth states is being pursued. Another aspect of particular interest is the synthesis of collagen, a specialized product of differentiated cells. This problem is being pursued through the use of heterologous cell-free systems. That the synthesis of collagen is initiated in such a system has been shown. This result has important implications to both the general topic of transcription and translation of genetic information as well as the more specialized topic of collagen biosynthesis. The Chief of the Cell Biology Section is currently assigned to the Medical Research Institute at Mill Hill, England.

The major contribution that the Laboratory of Biochemistry has made to medical and dental research through the training of postdoctorates and guest workers who are now located in leading laboratories throughout the world continues. These individuals provide a major source of innovative ideas as well as manpower to the Laboratory programs.

Research-related activities by members of the Laboratory include editorial board responsibilities by two persons, organization of a Gordon Conference, assignments to major laboratories abroad (already mentioned), teaching and administrative activities in the Foundation for advanced Education in the Sciences, participation by two persons on the Equal Employment Opportunity Advisory Committee, numerous reviews of manuscripts for several journals and grant applications from NIH and other agencies, and presentation of many papers at national and international meetings and in seminars inside and outside NIH.

An important organizational change was the formation of a Laboratory of Developmental Biology and Anomalies from the Connective Tissue Section and other laboratories. The remaining three sections, strengthened by the addition of several positions, now constitute the Laboratory of Biochemistry. These changes recognize the importance of the Institute's program in developmental biology and a shift in emphasis of the biochemistry program from protein chemistry to macromolecular structure.

Summary Report of Cell Biology Section
Laboratory of Biochemistry
National Institute of Dental Research

Background

The information stored in DNA is ultimately translated into the physiological activity of differentiated animal cells and tissues by way of RNA and protein. Studies in the Cell Biology Section aim at elucidating the biochemical processes by which this translation is achieved and controlled.

The work of the section is divided between two major aspects of this problem:

1. Studies correlating alterations in the differentiated state of the cell with changes in the synthesis and processing of various RNAs. What biochemical processes regulate such changes?

2. Studies on the activity, control, and organization of the protein synthesizing mechanism of the cell and their influence on the differentiated state.

Progress

Studies on Factors Controlling Lymphocytes Function

For several years, the RNA metabolism of human peripheral lymphocytes has been underinvestigation. These cells offer certain notable opportunities for research: their physiological activity *in vivo* includes prolonged periods of non-growth, followed by abrupt onset of growth in response to an immunologic stimulus. This sequence of events may be studied *in vitro* (1). The capacity to vary its growth rate in response to external stimuli may be viewed as an aspect of the differentiated function of the lymphocyte. An understanding of the biochemical mechanisms which control the growth of lymphocytes *in vitro* is viewed as having impact on two major problems in modern biology and medicine: 1) the control of cell growth *per se*; and 2) the regulation of cell differentiation.

Previous studies in this Section have established the patterns of RNA metabolism characteristic of normal, resting and growing lymphocytes [reviewed recently (1,2)]. In the course of these studies, alterations in RNA metabolism characteristic of the shift from the resting to the growing state have been identified (3,4). In particular, a previously underscribed mechanism of cell growth regulation, based upon the control of degradation of newly formed ribosomal RNA, was reported (5). The growth of resting lymphocytes is restricted by a process which limits the rate at which new ribosomal RNA can be accumulated. RNA molecules synthesized in excess of this limited amounts are degraded. Such "wastage" may affect more than half of the newly synthesized ribosomal RNA molecules (rRNA) in resting lymphocytes. That control of such wastage may be important in cell growth regulation is shown by the rapid reversal of such wastage following the onset of lymphocyte growth (6,8).

In a recent study (9), the process of rRNA degradation in resting lymphocytes was examined in detail. It was found that the two components of rRNA -28S and 18S rRNA's - are degraded independently in the nucleus at different times following their synthesis, despite their having been synthesized together as parts of a common precursor molecule. Thus, 18 molecules are degraded immediately after their formation, while 28S molecules synthesized at the same time are degraded only after a prolonged period of processing. It is apparent that a very precise control exists over the nuclear degradation of ribosomal RNA, which is consistent with the hypothesis that this degradation and its reversal constitute an important growth regulating mechanism.

These observations provided additional evidence that turnover of cytoplasmic ribosomes occurs in both resting and growing lymphocytes. Ribosomal turnover was distinguished from the "wastage" of ribosomal RNA described above because both 18S and 28S RNA's were degraded in parallel during turnover. It was found that a marked increase in half life of new ribosomes occurs after growth stimulation. However, careful analysis revealed that this was due to the accumulating ribosome content of growing cells, resulting from increased synthesis and decreased intranuclear wastage of rRNA. The absolute number of ribosomes degraded per unit time changed very little after growth stimulation. Thus, the degradative portion of the ribosome turnover process does not seem to be a major point of regulation in the control of lymphocyte growth.

Evidence was also obtained that the survival of newly synthesized ribosomal RNA molecules is dependent on the availability of proteins ("ribosomal protective proteins") which appear to protect the RNA from degradation (7,8). The number of such protein molecules available at any moment apparently determines the number of ribosomal RNA molecules which are protected; the remainder are degraded. Since normal cell growth is dependent on the accumulation of new ribosomes, control of the rate of synthesis of ribosomal protective proteins may be the means by which rRNA survival and degradation is determined, and hence may be critical in cell growth control.

We propose that ribosomal-protective-protein is one of the large complement of proteins of the ribosome. A major effort is in progress to isolate, this protein. It is being done coordinately in lymphocytes and in HeLa cells, the latter being used as a source of large quantitites of material. To date, ribosomes from normal growing lymphocytes and from HeLa cells have been isolated, their proteins separated and analyzed by acrylamide gel electrophoresis. Examination of the relative rates of synthesis of the various ribosomal proteins in rapidly growing lymphocytes is currently in progress. Results to date indicate that particular proteins show the

rapid labeling expected of a ribosomal protein whose production is rate limiting for ribosome assembly.

We have successfully developed the methodology for preparation from HeLa cells and from lymphocytes of large numbers of ribosomes and ribosomal subunits labeled with a variety of radioactive precursors. Degradation of these particles into smaller ribonucleoprotein components by controlled ribonuclease digestion has also been achieved. We have also made great progress in developing chromatographic techniques for isolating the specific

ribonucleoprotein fragment which bears the protein most likely responsible for protection of 18S rRNA. Ribosomal proteins prepared from this fragment are highly enriched for the desired protein(s). We anticipate characterizing these proteins in the near future and applying our results to the study of growth regulation in lymphocytes.

Simultaneously we are developing techniques for the separation of proteins from glycoproteins and of glycoproteins bearing terminal sialic acid residues from other glycoproteins. These methods will greatly facilitate purification of such proteins from all sources, and are potentially valuable tools for the immunologist. Such techniques will permit the ventual separation of ribosomal proteins associated with specific regions of ribosomal RNA. It will then be possible to study the activity of specific proteins in protection against ribonuclease attack, and in relation to other ribosome functions. Following the identification of the specific ribosomal protective protein(s) in HeLa cells, it will be feasible to study the synthesis of these proteins in relation to lymphocyte growth regulation.

Another major class of cellular RNA is the messenger RNA which transmits genetic information from DNA to ribosomes for translation into proteins. The means by which animal cells control the transcription of various messenger RNAs in the nucleus and their translation in the cytoplasm is a subject of study in many laboratories. The lymphocyte offers a unique opportunity for studying this process with great precision, since this cell undergoes differentiation in cell culture. Few laboratories in the world have taken advantage of this fact.

Using a newly-discovered biochemical property of messenger RNA in animal cells, i.e. the possession of an extensive polyadenylate segment, we have begun a study of the metabolism of messenger RNA in resting and growing lymphocytes (11). The kinetics of its nuclear synthesis, processing, and transport to the cytoplasm are currently being examined, together with growth-induced alterations. The distribution of mRNA among various compartments of the cytoplasm has been studied. One significant preliminary finding is an indication that the resting lymphocyte may transcribe and transport to the cytoplasm messenger RNA's which are not used to make proteins in the resting cell, but which are rapidly utilized when growth stimulation occurs. This may provide a clue to the mechanism by which the lymphocyte is able to respond so quickly to external stimuli.

To aid in these studies, a computerized approach to the analysis of the kinetics of RNA precursor pool labeling by radioactive materials was developed and applied to the study of RNA labeling in lymphocytes (10). This method permits the investigator to correct RNA labeling data for changes in precursor pool specific activity, without the necessity for measuring the pool specific activity directly. For work with lymphocytes, this is essential, because it has been shown that slow labeling of RNA precursor pools markedly influences the labeling of RNA.

In a related study, a unique double-stranded RNA widely present in animal cells was discovered (12,13) as well as a ribonuclease specific for double-stranded RNA localized in the nucleus (15) and cytoplasm.

The mechanism of action of an important antitumor drug, phleomycin, a member of the bleomycin-like drugs, was established inadvertently, as an out-growth of the aforementioned studies. The question was posed whether the mode of synthesis of double-stranded RNA was dependent on DNA synthesis and phases of the cell cycle, or was preplicated independently of proliferative events. An inhibitor of DNA synthesis was sought. However the drug which was used, phleomycin, appeared to stimulate DNA synthesis in isolated nuclei (16). On further examination, this putative inhibitor of DNA synthesis acted by causing breaks in DNA strands (17) and secondarily stimulated a futule DNA-ligase repair mechanism. The mechanism of action of the drug was established definitively using purified viral DNA.

Studies on Cell-Free Collagen Synthesis

Differentiated animal cell systems are often characterized by the production of large amounts of specific proteins. Such production varies not only among different tissues, but also during various stages of development of particular tissues. The means by which such differentiated states of protein synthesis are determined and maintained is being sought at the biochemical level by an analysis of the protein synthesizing elements in a cell-free system. This effort involves the cell-free synthesis of collagen.

Cell-free protein synthesizing systems have been established successfully using both Krebs II ascites tumor cells and wheat germ extracts as sources of ribosomes and other required factors. These systems have been used to translate the collagen messenger RNA (20,21).

Successful synthesis of complete collagen chains in the cell-free system has been achieved. Products of synthesis have been evaluated by molecular sieve and CM cellulose column chromatography and as suitable substrates for collagenase digestion and proline hydroxylation. Cyanogen bromide peptide chromatography is an additional procedure which is being applied currently to further identify the products of synthesis.

Work is also in progress to isolate the messenger RNA of collagen, using poly T cellulose column chromatography, cesium sulfate buoyant density and sucrose density gradient centrifugation. [^{32}P] labeled collagen mRNA is being characterized by digestion and fingerprinting techniques using column and thin layer chromatography.

The current source of collagen mRNA is the 16 day old chick embryo calvarium. This tissue devotes up to 60% of its protein synthetic activity to collagen production. A major question is whether this emphasis is based upon the proportion of mRNA devoted to collagen, or upon the extensive utilization of a small amount of mRNA. Evidence for the former possibility is being sought through attempts to label and isolate the collagen mRNA and mRNA-bearing particles from developing chick calvaria. The alternative possibility is being investigated in terms of the enzymes and transfer RNA molecules which are essential to the translation of the collagen mRNA. Rat chondrosarcoma, which synthesizes exclusively type II or cartilage collagen, has also been used successfully as a source of mRNA in cell-free synthesis.

The unique amino acid composition of collagen (high glycine and proline content) suggests that tissues active in the production of collagen may be enriched in the amino acylating enzymes and/or isoacceptor tRNAs required for those amino acids. Transfer RNA preparations have been isolated from chick calvaria and from liver as a control. A procedure has been developed for the separation of isoacceptor RNAs for proline glycine and arginine in order to determine whether enrichment for collagen-related amino acid isoacceptors is present. Initial studies in this determination suggest that such enrichment does occur.

An unrelated series of studies were conducted in collaboration with the National Eye Institute. Pilocarpine is the most important and most common drug used in ophthalmology. It is a miotic and an anti-glaucoma agent, and also causes the salivary gland to produce thick rope-like mucous secretions. In common usage, pilocarpine has also exhibited minor antagonistic effects shortly after the onset of its pharmacologic action. Studies were undertaken to rule out contamination by a minor component in commercial pilocarpine preparations which could explain this paradoxical atropine-like action of the drug (18). None was found.

The fate of pilocarpine and its mode of inactivation following administration has never been determined. We have established that the drug is inactivated by binding to a serum protein. This binding is reversed by mild heat treatment. Binding to the serum protein can be followed spectrophotometrically (19).

Significance:

Improved understanding in these fields is currently of great importance to contemporary Dental Research. Disordered growth and development of oral facial structures are major causes of pathology in this area. Since proper development depends critically on precise differential control of cell growth and non-growth, improved understanding of such control is vital to a reasoned approach to prevention and treatment. In addition, immune phenomena at the cellular level, involving lymphocyte reactivity to foreign and host materials and tissues, are now thought to play an important role in oral ulcerative disease and in periodontal disease, two widespread diseases of the American population. Since lymphocyte participation in these conditions is mediated through the growth response to specific stimuli, it is exceedingly important that we understand the means by which the lymphocyte recognizes, interacts with and responds to such stimuli. Only by knowing the steps in this sequence in great detail can we hope to intercede at the proper points to control lymphocyte responses for the benefit of the patient.

Perhaps of greatest significance is the relevance of these studies to the problem of oral cancer. A thorough understanding of the biochemical basis from the control of normal cell growth must underlie any rational attempt at prevention and non-surgical treatment of cancer. This is especially vital for oral cancer, since surgical treatment is often tragically disfiguring, so that the "cured" patient is hardly able to make use in any normal way of the years added to his life.

The orderly formation and placement of collagen is also essential to normal cranio-facial development. Studies on the cell-free translation of this key protein as well as studies of control mechanisms has clear relevance to NIDR goals. Much evidence indicates that the production of proteins is controlled, in part, by factors which act during the synthesis of the protein molecule. These factors, and their modes of action, have only begun to be understood, and that understanding has come only through the development of cell-free protein synthesizing systems. Application of this methodology to collagen biosynthesis will provide information as to the regulation of production of this protein at the most basic level. The possibility exists that such knowledge will permit us to intercede locally with appropriate biochemical treatment and correct problems of improper bone development in the jaw and other facial structures. Thus, malocclusions may eventually be amenable to biochemical intervention, providing a less expensive and more physiological approach to this problem than that currently in use.

In a more general sense, fuller understanding of the basic controls exerted over collagen synthesis will play a role in unraveling the causes of congenital cranio-facial anomalies. There can be little doubt that both environmental and genetically-determined developmental disorders result, in many cases, from deranged control of the production of specific proteins. Disordered regulation of collagen synthesis may be involved in the production of cranio-facial developmental anomalies and it is important to identify the particular biochemical steps which are susceptible to derangement, either through genetic defect, through toxic effects of the environment, or because of unusual stresses at critical times in uterine development.

Major progress has been made in this undertaking.

Future plans:

Work on cell-free translation of collagen mRNA will continue. Isolation and characterization of the collagen messenger will be followed by DNA-RNA hybridization experiments. This will answer some basic questions as to the nature of the differentiated state. What is the gene dosage of the DNA coding for collagen? Does it increase as tissue becomes committed to collagen synthesis? What is the half life of the collagen messenger RNA? Does it increase with increasing differentiation? For example, what mechanisms are used to amplify the genetic information of developing bone, cartilage, and other connective tissues?

Certain characteristics of the collagen messenger RNA can be predicted from the known structure of collagen. We will attempt to document these characteristics and then with greater confidence persue other properties of this important eukaryotic messenger RNA and the control mechanisms which are inherent to it.

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Summary Report of Connective Tissue Section
Laboratory of Biochemistry
National Institute of Dental Research

Background

Numerous human disorders involve connective tissue. These include developmental anomalies, inflammatory conditions, and tissue destruction due to aging, infection or other disorders. Major programs by the NIDR on dental diseases involve research in these areas.

It is the object of the Connective Tissue Section to apply new information on the chemistry and biology of connective tissue to disease states. In addition, we are studying acquired and inherited disorders of connective tissue to identify the underlying molecular defects and have taken on new initiatives in developmental biology.

Progress

Chemotaxis

Factors produced by bacteria that attract polymorphonuclear cells (PMN) by chemotaxis are being studied. While trying to isolate and characterize these substances, it became apparent that these factors were extremely heterogeneous and were probably small peptides. They have now been identified as n-formyl methionine peptides. The synthesis of a protein is initiated in bacteria with the formylation of methionine attached to a unique methionyl tRNA. Subsequently, other amino acids are added by standard reactions. n-Formyl methionine or n-formyl methionine plus additional amino acids are cleaved as a step in the processing of the protein. The synthesis of proteins in animal cells is initiated for the most part with methionine. This difference explains the unique class of molecules that bacteria produce and PMNs detect. Further, this may be a more general informational system, since it has also been found that macrophages are attracted to n-formyl methionyl peptides.

Diseases of Connective Tissue

Inflammatory disease. Previously we had found that macrophages produce collagenase when activated by exposure to endotoxin. Now we have found that sensitized lymphocytes secrete lymphokines which can also activate macrophages. This result may explain the mechanism leading to the destruction of collagenous structure in inflamed tissue. In this schema, lymphocytes would respond to a foreign antigen to which they are sensitive by undergoing blast transformation. Soluble factors are thus produced by the activated lymphocytes which attract macrophages to the tissue by chemotaxis. Subsequently, the lymphokines activate lytic mechanisms in the macrophage, including collagenase synthesis.

Tissue Specific Collagens and Disease

Recent studies by others have demonstrated the occurrence of various genetically distinct collagens. These include the major protein in the body, type I collagen; the cartilage collagen, type II; "fetal" or blood vessel collagen, type III; and basement membrane collagen.

We have now isolated types I and III collagen and procollagen and characterized these proteins. Further, cells from human skin have been found to synthesize both type I and III collagens in culture, although type I accounts for some 90% of the total. Interestingly, cells from certain patients with very severe forms of osteogenesis imperfecta have been found to synthesize much more type III collagen than normal. It appears that type I collagen synthesis is defective in these cells and possibly in these patients. These observations may account for the defects observed in their bones and certain other tissues.

Significance

While connective tissues were once considered to be metabolically inactive, it is now known that synthetic and degradative processes in these tissues undergo marked alterations in response to physiological stimuli and disease processes. We have attempted first to understand the steps in the formation and development of the major structural components of connective tissue, and second to apply this information to diseases affecting these tissues. In the past, particular attention was directed to experimental disorders. Using techniques developed during the study of these conditions, several significant advances have been made in the understanding of inherited and acquired disorders of connective tissues in humans.

The directed migration of cells is a general biological response which is important in development, host resistance and repair. Methods used to study the chemotaxis of PMN leucocytes may be applicable to other cell types and may be essential to the understanding of a variety of cellular reactions.

Future Plans

As a result of recent organizational changes, the Connective Tissue Section is to be included in the Laboratory of Developmental Biology and Anomalies. This change will have considerable influence on the direction of future research by the Connective Tissue Section. In particular, more attention will be directed toward developmental defects, both drug induced and genetic. However, basic studies will be continued on connective tissue to build the scientific base for more applied work. In particular, we will continue the study of inherited diseases of connective tissues in humans. Some attempts will be made to understand basement membrane protein. A major effort will be initiated to clarify the synthesis of collagen using cell free synthesis. This latter effort should be useful in understanding fibrosis as well as development of connective tissue structure.

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Summary Report of the Enzyme Chemistry Section
Laboratory of Biochemistry
National Institute of Dental Research

Background

Studies carried out over the past several years have been directed toward characterization of enzymes, termed transglutaminases, that are responsible for the formation of γ-glutamyl amide bonds in proteins and polypeptides. These enzymes catalyze transfer reactions at the carboxamide group of peptide-bound L-glutamine with a high degree of stereospectificity (for review see (1)). In the presence of acceptor amines, the transfer reaction results in the formation of substituted amides ($-CONH_2 + RNH_2 \rightarrow -CONHR + NH_3$).

One of the well-characterized covalent cross-links between and within protein molecules is the ε-(γ-glutamyl)lysine bond. There has been increasing fibrin clots, cell membrane glycerinated myofibril of muscle, proteins of seminal plasma, native wool keratin, and the citrulline-containing protein fraction of hair (for review see (1)). The wide occurrence and obvious importance of γ -glutamyl amide bonds has led us to focus attention on the enzymes responsible for their formation.

Progress

The transglutaminases isolated from red blood cells have been studied kinetically and immunochemically. The enzymes from human and guinea pig erythrocytes display identical kinetic properties which are also identical to those of the guinea pig tissue enzyme. These red blood cell enzymes cross-link fibrin by means of ε-(γ-glytamyl)lysine bonds and catalyze formation of a single ε-(γ-glutamyl)lysine bond in the hemoglobin molecule (2). The human red blood cell enzyme shows cross-reactivity with rabbit antiserum to the guinea pig liver enzyme(3).

In addition to the three major classes of transglutaminases defined by earlier studies in this laboratory (1,4,5) a further distinct class of these enzymes has been found in mammalian seminal plasma. These enzymes, which coagulation of seminal plasma. The origin of the enzymes is the prostate gland from which they have been isolated in the guinea pig and human. One has a molecular weight of 180,000 to 200,000, exists in the active form, and displays a specificity similar to that of the tissue transglutaminase. The other, of molecular weight 160,000, exists as a zymogen that is activiated by thrombin. Each enzyme requires Ca^{2+} for activity and coverts soluble blood fibrin to insoluble or stabilized fibrin by ε-(γ-glutamyl)lysine cross-link formation.

A number of molecular properties of human plasma protransglutaminase (blood coagulation factor XIII) and of the active enzyme (factor XIIIa) formed by thrombin activation have been determined. Several properties of the protransglutaminase from blood platelets have also been investigated. These include: a) The disulfide - sulfhydryl distribution in the subunits of the

plasma zymogen. The catalytic subunits (a chains) contain 12 -SH groups per molecule and no disulfide bonds. The noncatalytic subunits (b chains) have no -SH groups, but contain 32 to 34 disulfide bonds per molecule (6); b) The subunits of the plasma zymogen have been separated. The noncatalytic subunits may be combined with platelet zymogen to form a zymogen indistinguishable from that of the plasma: c) An active site group of the plasma and platele enzymes has been identified as an -SH. The stoichiometry of inactivation of the enzymes by [^{14}C]iodoacetamide and by 3-nitro-4-hydroxy-α-bromoacetophenone shows that total loss in enzymatic activity is accompanied by incorporation of one mole of inactivator per molecule of enzyme. These findings suggest that both enzymes catalyze their reactions by a so-called "half-of-the-site" reaction requiring participation of a subunit structure for catalytic activity (6,7); d) The plasma zymogen is not dissociated by Ca^{2+} and remains as a tetramer structure containing 2 a chains and 2 b chains. Upon activation by thrombin in the absence of Ca^{2+}, the enzyme is found also to be a tetramer containing 2 b and 2 modified a chains. However, when Ca^{2+} is added to the active enzyme it dissociates into a chain dimers and b chain dimers (6). The dissociation constant for Ca^{2+} estimated from the requirements for this dissociation (1 to 2mM) is close to that determined from Ca^{2+} in its function as an activator for the amine incorporation reaction (8). This suggests that it is the a chain dimer, dissociated from b chains, that is catalytically active; e) The subunits of thrombin-activated plasma transglutaminase have been separated by gel filtration in the presence of Ca^{2+}. Removal of Ca^{2+} has been shown to result in reassociation of the subunits to form a tetramer indistinguishable from that found in the absence of Ca^{2+}; f) The zymogen from platelets (a_2) is activated by thrombin at a significantly faster rate than that from plasma (a_2b_2). A proenzyme prepared by combining the isolated b chain dimer from plasma enzyme with platelet zymogen was found to be activated by thrombin at the same rate as the plasma zymogen. This is substantial evidence that protransglutaminase b subunits function to control the rate of enzyme formation by thrombin.

The Ca^{2+} requirement for catalytic hydrolysis and transfer of active esters by plasma and platelet transglutaminases has been examined. It was surprising to find that this requirement (K_a, Ca^{2+} 50mM) is significantly higher than that for amine incorporation at glutamine residues. The opposite has been found to be true with the tissue enzyme (9).

Active site mapping studies of transglutaminases, commenced last year, have been extended with particular emphasis on the tissue and blood enzymes. Earlier fundings using straight- and branched-chain aliphatic amides indicated that glutamine substrate attaches to the enzymes with its β and γ methylene groups situated in a hydrophobic binding region and with its carboxamide group directed toward the active site -SH group of the enzyme (1)). The dimensions of this binding cleft on the enzymes were estimated from atomic model studies to be about 5A X 5A. Evidence has been obtained from inhibitor and kinetic studies that the enzymes undergo a conformational alteration at some step during catalysis, probably proceeding or together with enzyme acylation.

These findings with aliphatic amides have been confirmed by using peptide derivatives of methylglutamine isomer (11). That the derivatives of L-α-methylglutamine only are substrates for transglutaminases is strong evidence for the postulated active sites. The observations with the methylglutamine derivatives have also formed the basis for a theory as to how the enzymes exert their stereospecificity, i.e., their strong preference for L-glutamine residues. This follows from the suggestion that peptide-bound L-glutamine residues are oriented on the enzyme surface with their α-hydrogen projecting away from the surface. In the case of D-glutamine residues the α-hydrogen, abutting the enzyme surface, perturbs the normal mechanism.

A corollary to inhibition studies carried out in conjunction with active site mapping work has been the development of a general theory for inhibition in the case where inhibitor is present in constant proportion to variable substrate (12). The presentation of this theory should be of special value to investigators designing inhibition experiments. Further, this theory will enable workers to recognize inhibiting impurities in substrate preparations. This theory further generalizes the concept of non-productive substrate binding and simplifies the recognition and interpretation of this phenomenon.

A series of heptapeptides of the general structure, X-X-X-L-gln-X-X-X, where X is glycine or L-leucine and L-gln is L-glutamine, have been prepared. The formylated derivatives of these peptides have been tested in an effort to gain evidence that transglutaminases have an extended active site, and that the variations in specificity of the various classes of enzymes are a function of the amino acid residues surrounding the glutamine residue; the findings to date are very encouraging, and indicate pronounced effects of hydrophobic residues as far as three amino acid residues away from the glutamine. Reporter group studies are being conducted in conjunction with these activity investigations. Design and preparation of inactivator compounds that will report the position of hydrophobic binding sites are underway.

Active site mapping has been extended to studies on the primary amine binding sites in the acyl transglutaminases. As in the case of glutamine residues, there is a pronounced stereopreference for the ε-amino groups of L-lysine residues in peptides. Peptides containing L-lysine residues are bound approximately 5 times more tightly to the acyl enzymes than are those containing D-residues of lysine.

Significance

A comprehensive study of various transglutaminases has shown that the enzymes are widely distributed in various organs and tissues, and that they may all be involved in the formation of ε-(γ-glutamyl)lysine crosslinks within and between protein molecules. These linkages are essential in maintaining the permanent rigid structure of many protein molecules.

The physiological importance of the protransglutaminases of plasma and platelets is well known. The finding of protransglutaminases in placenta and uterus indicates another regulatory control site of the blood coagulation process. Estrogen and progestrone regulation of transglutaminase levels in rabbit uterus has been observed (13).

Understanding of the molecular characteristics of the transglutaminases is vital to determination of the function of these enzymes in normal and diseased tissues, pharmacological control of activity and hormonal regulation.

The minimal substrate structural requirements for liver transglutaminase have been defined over the past year through the studies described above. We now have a better understanding of the mechanism of enzyme-substrate interactions in transglutaminase-catalyzed reactions. The technique of active site mapping, using straight and branched chain substrate analogs, methylglutamine isomers, D- and L-lysine peptides and large glutamine and lysine peptide derivatives, is one which will be applied to studies with other taansglutaminases and most certainly will reveal similarities, as well as differences, in the members of this important group of enzymes.

Future Plans

Preliminary studies suggest a primary role for transglutaminases in wound healing (for review see (1)). Attention will be focused on the possible interaction between fibrinogen and collagen as catalyzed by transglutaminases and the possible relationship of this interaction to wound healing.

The interrelationship between the fibrinolytic enzyme, plasmin, and transglutaminases may be of prime importance in chronic inflammation. Studies will be directed toward examining the influence of transglutaminase-catalyzed cross-linking on plasmin degradation of a number of structural proteins.

The possible use of liver transglutaminase in localizing and determining the orientation of membrane proteins and other structural protein is under investigation.

Studies of the effect of various amino blocking groups on the reactivity of model peptide substrates will be continued. The effect of various metal ions on these activities of transglutaminases will be investigated.

There are plans to expand the substrate specificity studies described to some of the other transglutaminases currently under investigation in this laboratory.

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Summary Report of Protein Chemistry Section
Laboratory of Biochemistry
National Institute of Dental Research

Background

Collagen is the major structural protein of all vertebrate and many invertebrate species. It is found not only in the major connective tissues, skin, tendon, bone, and cartilage, but is an important component of tissues such as basement membranes, cornea and blood vessels. The basic structure common to the major and many minor collagens is a rod-like molecule about 3000 x 15A composed of three polypeptide chains each with about 1000 amino acids. The major collagens of skin, tendon and bone (type I collagen) contain two kinds of chains (two $\alpha 1$ and one $\alpha 2$ chain) but other collagens have three identical chains that appear to be closely related to the $\alpha 1$ chain of type I collagen.

The collagen molecule is triple-helical throughout most of its length. However, the N- and C-terminal 15-25 amino acids do not have the characteristic amino acid sequence of the helical portion of the chains and therefore have a different structure. Covalent cross-links, derived from lysine residues, originate in these regions. They may also have other functions.

Collagen functions biologically as the fibril, an ordered rope-like array of molecules several hundred to several thousand angstroms in diameter. These fibrils are arranged in various ways characteristic of the tissue. At this level of structure, other constituents of connective tissue play important roles. These constituents vary with the tissue but often include elastin, the proteoglycans and mineral.

Connective tissue studies therefore involve not only chemical and structural investigations of the various constituents but also interactions between them. The study of interactions is highly dependent on a detailed knowledge of chemistry and structure.

Progress

Certain aspects of the broad problem outlined above are being emphasized in the current program of the Section. These aspects together with recent progress are discussed separately.

1. Heterogeneity of the $\alpha 1$ chain as expressed in the chromatographic behavior of $\alpha 1$-CB6, the C-terminal cryanogen bromide peptide, has been observed. We have shown that the peptide $\alpha 1$-CB6 has two chromatographic forms when isolated from salt-extracted rat skin collagen. At least four forms are present in samples prepared from urea-extracted collagen. We have devised methods to separate the various forms. The place in the sequence where differences occur is presently being sought by preparing and characterizing smaller fragments such as the chymotryptides.

2. The packing of collagen molecules into fibrils requires that specific cross-link sites be present in the helical part of the molecule as well as in the already characterized N- and C-terminal cross-link regions. The positions of these helical sites are being sought by isolating double-chain peptides containing a cross-link after cyanogen bromide cleavage of insoluble collagen. A peptide of this type has been isolated consisting of α1-CB6 and (probably) α1-CB1. Chymotryptic cleavage shows that the helical cross-link site in α1-CB6 is in the chymotryptide designated C1. The extract residue is being identified. This finding is significant since it provides a critical test of molecular packing models of the collagen fibril.

3. Soluble collagen as normally isolated is known to be altered by proteolytic cleavage of the C-terminal nonhelical region. The results of various chemical and physical chemical studies using these preparations may therefore be effected by this alteration. Of particular interest are studies of fibril formation where the N- and C-terminal regions may play critical roles in directing aggregation. Methods to prepare intact soluble collagen are therefore being sought. We have found that acid extraction in the presence of pepstatin, an acid protease inhibitor, produces a collagen that by preliminary tests appears to be intact. This collagen preparation is being characterized in more detail.

4. Although most collagens that have been studied have the same basic molecular structure, other collagens or collagen like proteins are known that have quite different structures in that large parts of the molecule are noncollagenous. These include procollagen (the biosynthetic precursor of collagen), C1q (a complement component), possibly some of the basement membrane collagens, and certain invertebrate collagens. One in the last group is Ascaris cuticle collagen. We are presently studying this protein to gain a better understanding of these "unusual" collagens. We have found that the reduced denatured protein contains three different chains that can be separated chromatographically. They all have collagenous and noncollagenous portions and molecular weights of about 60,000 (compared to 95,000 for the α chains of the common vertibrate collagens). The relative amounts vary widely in different samples suggesting that they are derived from three different collagens rather than from one collagen with three different chains.

5. Well-characterized cyanogen bromide peptides from collagen provide useful model systems for physical chemical studies of molecular structure. One such peptide is α1-CB2 which has 36 residues and will make a triple-helical molecule in solution. We have undertaken a study of its structure using ^{13}C nuclear magnetic resonance. It was found that the typical solution spectrum of the denatured peptide changes markedly when triple helix is formed. The changes can be interpreted in terms of interactions between specific atoms and side chains and reveal details about molecular structure (1).

6. The completion of the primary structure of the α1 chain of collagen through the efforts of several laboratories has permitted a preliminary test of theories of fibril formation. Since electrostatic and hydrophobic interactions are fundamental to many protein interactions, it would be expected that opportunities for these interactions to occur would be maximal when two collagen molecules are associated in the normal stagger relationship postulated for the collagen fibril. We have found by computer analysis of the sequence that interactions are maximal when molecules are staggered by multiples of 234 amino acid residues (2). Since electron mocroscopy and x-ray diffraction has shown that collagen molecules are staggered by 670A, this results permits a more detailed definition of the relationships between molecules in the fibril. Further analysis in three dimensions may reveal additional details about molecular packing at the atomic level.

7. Another approach to the problem of molecular packing has been taken by comparison of the primary structure with the band pattern seen in electron micrographs of stained native collagen fibrils and other polymorphic collagen aggregates. We have found that the distribution of charged groups as seen by staining of native fibrils corresponds exactly to the distribution predicted from the positions of charged amino acids in the sequence and the expected molecular packing in native fibrils (3). This relationship has also permitted us to show the relationship between collagen molecules in a polymorphic form in which the collagen fibrils have a symmetric band pattern.

8. Analysis of electronmicrographs of another polymorphic form of collagen aggregate has allowed us to obtain independent evidence for a substructure within the native collagen fibril (4). In this polymorphic form, narrow subfibrils with the native band pattern are associated in a step pattern producing obliquely-banded fibrils. Analysis of the micrographs shows that the subfibrils vary in width. The narrowest has a diameter of 40A. Since it also has the native 670A period, the number of ways that collagen molecules can be packed into a fibril are severly restricted. The five-stranded Smith microfibril, which is a regular helix of collagen molecules (or another closely related structure), is the only simple structure that satisfies the results. This and related results permit a fairly detailed picture of fibril structure to be constructed (5).

9. Elastin is a major connective tissue protein in some tissues. It has the properties of a rubber. The molecular basis of the elasticity has not been clear. We have shown by ^{13}C nuclear magnetic resonance that like rubber the polypeptide chains of elastin in the solid state are in rapid motion almost as if the polypeptide chains were in solution (6). This result strongly suggests that standard elastomer theory as applied to rubber is also appropriate for elastin and that the molecular basis for elasticity is the same for elastin and rubber.

Significance

Since collagen is the major structural protein of connective tissues including teeth, bone and supporting oral structures, a knowledge of its chemistry and structure is necessary to an understanding of normal func-

tion. This understanding will permit a rational approach to the understanding and, thereby, to the prevention and treatment of connective tissue diseases. These include caries and periodontal disease, the major disease of oral tissues.

Progress along these lines has led to major programs in many laboratories studying orthopedics, dermatology, rheumatology, genetic disorders, calcification, wound healing, inflammation, ageing, pulmonary disease and oral disease. It can be predicted also that fundamental studies of collagen chemistry and structure will be critical to an understanding of collagen-cell interactions. These interactions occur, for example, in platelet response to wound healing and in several (perhaps most) developmental processes.

Future Plans

No fundamental changes in direction are planned. However, a shift in emphasis from chemical to structural studies, already occurring, will continue. It is planned to utilize the chemical and biosynthetic knowledge of connective tissue components in the study of higher level structure and of macromolecular interactions. To accomplish this, increasing reliance will be placed on biophysical and ultrastructural methods.

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Summary Report of the Laboratory of Biological Structure
National Institute of Dental Research

Despite continuing constraints on personnel and facilities and despite a certain amount of uncertainty generated by a proposed reorganization of the Laboratory described in more detail below, the Laboratory has continued to maintain a gratifying level of research accomplishment. The research has covered a broadly based series of basic and applied investigations, all with the common goal to facilitate understanding of a variety of normal and abnormal biological processes affecting oral health. As in prior years, progress for the year is reported in the sectional summaries which follow.

During the reporting year the professional staff of nine senior investigators, two staff fellows, and one research associate have submitted seventeen manuscripts and ten abstracts for publication. In addition, members of the staff have participated in national and international meetings and workshops; in editorial tasks; and in scientific review functions relating to NIH and other granting agencies. Members have also been active in scientific organizations and have played an important role in the setting up of a Mineralized Tissue Group within the International Association for Dental Research.

This year will be the last year of operation for the Laboratory of Biological Structure in the sectional makeup represented in the following summaries. Only two of the sections, i.e., Experimental Morphology and Molecular Structure will remain in the laboratory. This means a consolidation of the functional mission to the program areas of mineralization and salivary gland function which historically have been the principal interest of the laboratory. The task ahead will be to strengthen efforts in these areas through the addition of appropriate manpower and through close interaction and collaboration with the other basic science laboratories of the National Institute of Dental Research, especially the Laboratory of Biochemistry and the Laboratory of Developmental Biology.

Summary Report of the Experimental Morphology Section
Laboratory of Biological Structure
National Institute of Dental Research

The basic objectives of the Experimental Morphology Section are to advance knowledge concerning the structure and function of normal and experimentally altered tissues and cells. Light and electron microscopy, electron diffraction, microradiography, enzyme cytochemistry, extra-and intra-cellular tracers as well as specific chemical detection methods are the principal technique which are used.

Studies presently underway include: (1) the effect of tetracycline and sodium fluoride on tooth development in the rat; (2) the basis for the precocious eruption of the incisor in newborn rats receiving epidermal growth factor; (3) ultrastructure and cytochemistry of salivary glands and (4) biochemical and ultrastructural studies on tissue fixation by protein crosslinking reagents. Progress in three of these areas will be described in more detail in this summary report.

To date our experiments have shown that in both young and old rats the effect of tetracycline hydrochloride (TC) on tooth development is directly related to the total dose. They have also shown that the effect varies with the age of the animal and with the concentration at which the drug is administered. In addition our studies have confirmed previous observations by Australian investigators that the molars are more sensitive to tetracycline than the incisors in the same animals. Further, consistent variations are observed in the severity of the response between different surfaces of the first and second molar.

Measurements of serum concentrations revealed that the level of tetracycline in the blood increased as the dose increased. Comparisons between animals which received the same dosage of tetracycline in concentrations of either 12.5 mg/ml or 25 mg/ml showed significantly higher serum levels in both young and old animals which received the more concentrated solution. On the other hand, no differences were observed in serum levels between young and old animals one and two hours after they received identical dosages of the antibiotic in identical concentration. Six and twentyfour hours after administration, however, the levels were significantly higher in the young animals, yet it was the old animals which exhibited the higher incidence of gross lesions. This finding coupled with the observed differences in response between molars and incisors of the same animal as well as between various surfaces of a single tooth indicate that local factors may modify the effect of the toxic agent.

Although complete data are lacking, our observations suggest that the rate of formation of the enamel is faster in the molars than in the incisors of the young animal, and faster in the incisors of the old than of the young rat. In addition it has been shown that the distance between the capillaries and the ameloblasts is less in the molars than in the incisor of the rat, an observa-

tion which also has been related to the enhanced metabolic state of the molar ameloblast. The existence of local variations in blood supply has not been established, nor is it known if the rate of enamel formation differs between various surfaces of the same tooth. However, on the basis of the observations mentioned above, it is possible that variations in tissue distribution of the drug and in metabolic state of the odontogenic cells may play an important role in determining the effect of the antibiotic on the developing tooth.

Future studies will be aimed at studying the effect of sodium fluoride on tooth development in the rat. In addition, the cell changes which underlie development of tetracycline and fluoride-induced defects will be investigated. Further,post-eruptive changes in the enamel of hypoplastic teeth will be studied, and the response of hypoplastic teeth toward a cariogenic challenge will be investigated.

Systematic morphological examination of the salivary glands is being undertaken so as to provide a clearer understanding of the correlation between structure and function in secretory cells. Although the major portion of the investigation is conducted on the rat parotid gland, other salivary glands and related exocrine organs are utilized when it is felt that they may provide additional information or serve as a particularly suitable model system.

Our most recent studies of the salivary glands have been designed to achieve a number of specific aims. Among these is the characterization of the structure and cytochemistry of the Golgi apparatus in acinar cells. Most of this work was done on the rat lacrimal gland, since this gland has a cytochemically demonstrable secretory peroxidase activity, which is relatively resistant to fixation. The results indicate that the morphology of the Golgi apparatus of these cells is essentially the same as that of the parotid gland, and that the distribution of the enzyme secretion product (and therefore the probable flow of secretory proteins through the Golgi apparatus) is also the same. In accordance with current theories of secretory protein transport and packaging, peroxidase in the lacrimal and parotid gland appears to move from the endoplasmic reticulum to the Golgi apparatus via small vesicles. As it moves from the outer face of the Golgi to the inner face it increases in concentration and accumulates in condensing vacuoles forming from the inner Golgi cisternae.

Another aspect of the salivary gland study involved exploration of the cytochemistry and function of peroxisomes. Our main emphasis has been on modifying existing cytochemical techniques in order to provide additional methods for studying the enzyme content of peroxisomes in various cells. Using rat liver as a model system, it was found that formaldehyde fixation retains substantial enzymatic activity, and that the enzyme is most active with glycolate as substrate. Since the reaction product is copper ferrocyanide, the application of the diaminobenzidine amplification method reported elsewhere increases the density of the reaction product and the sensitivity of the method, while enabling one to use shorter incubations with a consequent reduction in nonspecific deposits. Using these modifications, reaction product is essentially confined to hepatocyte peroxisomes, and we are now ready to try the method on other tissues.

In our continuing studies of tissue fixation by protein crosslinking reagents, our efforts have been concentrated on a comparison of the fixation and retention of glycogen in rat liver with dimethyl suberimidate (DMS), gluteraldehyde and formaldehyde. Initial histochemical observations of PAS-stained liver sections suggested that DMS retains more glycogen than either of the aldehyde fixatives. In addition, it yields a more uniform distribution throughout the fixed blocks without producing a background Schiff reaction due to the introduction of aldehyde groups with the fixative. Quantitative measurements of glycogen in fixed blocks, however, revealed that about 81% of the initial liver glycogen was retained with formaldehyde, 79% with glutaraldehyde, and 73% with DMS. We were never able to recover 100% of the glycogen, and since at most only 1-2% was lost into the fixative fluid, we presume that during fixation, glycogen is metabolically degraded until protein denaturation and enzyme inactivation is completed. Extracting fixed liver blocks in a manner which simulated the aqueous extraction that sections are exposed to during processing and staining show that 59% of the initial glycogen remains with the protein pellet after DMS fixation, the rest being extracted by water. In contrast only 35% and 25% of the initial glycogen is retained after glutaraldehyde and formaldehyde fixation, respectively. These results confirm the histochemical observations, and suggest that DMS may be useful as a fixative for the study of glycogen and other substances where Schiff stains are used.

Future plans are to continue the work described above. In addition, new studies will be initiated concerning the histochemistry and ultrastructure of Von Ebner's glands. Also under consideration is a developmental study of lipase and amylase activity in the tongue.

Summary Report of the Experimental Pharmacology Section
Laboratory of Biological Structure
National Institute of Dental Research

The section is studying the normal and abnormal development of the craniofacial complex in animal models.

Normal craniofacial development is being investigated by *in vitro* techniques in order to establish molecular events and determine the effect of exogenous agents on these events.

In the past we have been able to induce the malformation of cleft of the secondary palate by a variety of agents such as: Vitamin A, lathyrogens and benzhydrilpiperazines; however, this malformation has always been associated with other skeletal anomalies. In the past year we have finally been able to induce *cleft palate alone* in the Sprague Dawley rat by the administration of specific phenothiazines at critical stages of organization.

Administration of *cyclophosphamide*, at specific times of gestation can produce, either generalized or discrete craniofacial malformations in rats and rabbits. In the latter species, *cleft lip* has also been induced. At the present time studies are being carried out to determine the distribution, metabolism and possible activation of cyclophosphamide in various maternal and embryonic tissues.

Until the present time it was the consensus of opinion that the *pre-implantation* embryo was not susceptible to teratogenic agents. This is now being questioned. In order to explore the problem a project was started last year to develop a system for direct manipulation of the pre-implantation embryo, including determination of (a) *in vivo* factors in endocrine and drug-induced control of development and implantation, (b) methods of *in vitro* development and *micromanipulation* of embryos, (c) techniques of interstrain or intraspecies transplantation of embryos; and finally (d) the determination of critical biochemical parameters involved in DNA replication and RNA transcription which are related to factors of embryolethality and sensitivity to teratogenesis.

The importance of cell proliferation in anomalous development of craniofacial structures in general, and the primary and secondary palate in particular has not been determined. In addition, drugs which appear to interfere with craniofacial growth are administered relatively early in gestation, when the small size of the developing head precludes direct dissection and quantitative analysis. For this reason, new methods for determining *growth rates* are being developed. One of these methods involves administering labeled thymidine on days 9-15 of gestation and measuring the specific activity of the *DNA* in various embryonic regions as well as in the whole embryo on day 16. To define the length of isotope administration, the metabolic half life of thymidine is also being measured for each mode of administration. The relative growth of any region can then be determined by comparing their specific activity to the whole embryo, in both control and experimental groups.

The appearance of heterotopic cartilage in the palatine shelves as a result of Vitamin A treatment is also being evaluated. This is being accomplished by following the synthesis of collagen, acid mucopolysaccharides and glycoproteins, both in vitro and in vivo, in Vitamin A-treated and control embryos.

Previous work has shown that the Epidermal Growth Factor (EGF) inhibits epithelial cell death in palatal shelves cultured in vitro. Electron microscopic examination of the midline epithelial cells has revealed that the treated cells were actively undergoing the initial stages of keratinization, rather than dying as they normally would. The epithelium and the mesenchyme are now being separated by proteolytic enzymes and further experiments are being conducted to determine the effect of EGF on the synthesis of proteins, glycoproteins, acid mucopolysaccharides and on the levels of cyclic AMP in these two regions of the palate. Radioactive precursors are being used to selectively label cellular components and the results are being evaluated by autoradiography, SDS gel electrophoresis and quantitative biochemistry. Similar techniques are being used to determine the chemical nature of the glycoproteins which are secreted to the cell surface of the medial edge of the secondary palate prior to fusion.

In conclusion, the work of the Experimental Pharmacology Section has centered on studies of the pathogenesis of various types of drug-induced craniofacial anomalies in a variety of laboratory animals and on the normal developmental processes. In addition, studies have been initiated to determine the role that certain extracellular macromolecules play in palatogenesis. The work of the section has resulted in seven presentations at scientific society meetings and the publication of six papers.

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Summary Report of the Molecular Structure Section
Laboratory of Biological Structure
National Institute of Dental Research

The principal objective of the Molecular Structure Section is to study the structuro-chemical properties of calcified tissue, its collagenous and mineral components, and related synthetic systems. As in past years, research efforts were primarily divided between investigations on mineralized connective tissues per se and on synthetic analogues to the calcium phosphate salts investing these tissues.

Amorphous calcium phosphate (ACP) is an important component of hard tissue and a precursor to biological apatite. The chemistry, morphology, and kinship to apatite are beginning to be fairly well understood, but the spatial configuration of the ions in ACP is unknown. Conventional crystallographic techniques for studying solid-state structure cannot be applied to ACP as this substance does not possess long-range periodic order. An infrared, far infrared and laser Raman spectroscopic study of mixed anionic and cationic amorphous salts completed during this past year reduced, however, the number of possible spatial configurations to two alternatives: (1) a random packing of unit coordination structures of constant chemical composition and fixed bonding relationships, or (2) a random network of coordination complexes whose exact composition and structure vary from site to site.

Even though the structure of ACP is open to question, the pivotal role of this substance in biological mineralization is becoming increasingly indisputable. A study on the deposition of calcium phosphate from balanced salt solutions suitable for use in tissue culture experiments showed that ACP was formed at calcium and phosphate concentrations comparable to those found in serum and extracellular fluids. Thus most physiological fluids possess the potential to induce amorphous mineral formation de novo. The fact that they don't, except in connective tissues undergoing calcification, suggest that these fluids possess agents inhibitory to mineral nucleation.

Once initiated, however, the mineralization of connective tissue proceeds until the accreted calcium phosphate salts form a dense, compact mass. Such concentrated deposition cannot be accomplished by de novo precipitation from physiological fluids alone, but requires a pre-existing substrate. Matrix collagen has been implicated as a necessary substrate for compact mineral deposition, but not to be overlooked is the role of already existing apatite crystals in governing the density and spatial arrangements of newly formed mineral. Studies have been undertaken to assess the in vitro conditions under which new calcium phosphate material can be deposited onto synthetic apatitic substrates. Preliminary results have shown that the introduction of apatite seeds into supersaturated calcium phosphate solutions strongly modifies the mechanisms by which new apatite crystals can form in these solutions.

In addition to the above described investigations into the depositional alterations induced by apatitic substrates, studies were conducted to establish the effect of ion adducts on the composition of solution-prepared apatites. It was found that both the OH^- and HPO_4^{2-} content of non-stoichiometric apatites decreased with increasing fluoride content, with the ancillary effect of lowering the pH of the preparative solution. Another anion, more potent than fluoride in displacing HPO_4^{2-} from apatite, was pyrophosphate. On the other hand, monofluorophosphate was not a chemical modifier. In fact, apatites exposed to monofluorophosphate solutions adsorbed negligible amounts of this anion. Apatite, however, did catalyze the solution hydrolysis of monofluorophosphate into orthophosphate and free fluoride. Commercial sodium monofluorophosphate, such as is used in dentifrices, contains small amounts of free fluoride and condensed phosphate (pyrophosphate). The strong interaction of fluoride and condensed phosphate with apatite as opposed to the weak affinity of monofluorophosphate for this calcium phosphate suggests that these contaminating ions may be responsible for some of the effects on apatite previously ascribed to monofluorophosphate. The data also suggest that the caries-reducing effect of monofluorophosphate probably results from the action of the fluoride and condensed phosphate contaminants, supplemented by fluoride released from enamel-promoted hydrolysis of the monofluorophosphate.

Raman laser studies demonstrated that the compositional alterations in apatites induced by fluoride is also reflected by a change in crystallographic form. The low-symmetry monoclinic form of stoichiometric hydroxyapatite reverts to the high-symmetry hexagonal form of fluorapatite upon the addition of as little as one F^- ion per ten OH^- ions. These traces of F^- probably disorder the OH^- columns in the structure which results in a statistical favoring of hexagonal symmetry.

Infrared, Raman, and electron spin resonance spectroscopic studies on amorphous and apatitic calcium phosphate-macromolecule complexes were continued during the past year. Results from measurements on synthetic polyamino acid-mineral complexes showed that the mineral calcium bonds to aspartyl and glutamyl carboxyl groups and to prolyl and hydroxyprolyl carbonyl groups whereas the mineral phosphate bonds to lysyl, histidinyl and arginyl nitrogen. Therefore proteins like collagen appear to have several potential sites of attachment to mineral. The electron spin resonance spectroscopy was done in collaboration with Dr. I. Pullman and associates at New York Medical College.

As part of a continuing study on the quantitative x-ray diffraction properties of hydrazine-deproteinated bone mineral, the effect of tetracycline on developing bone was investigated. The results indicate that tetracycline retards mineral maturation in the growing rat skeleton.

Studies on fossil bones, conducted to assess the end results of possible postmortem alterations in skeletal tissue, indicated that the bone mineral had transformed to non-physiological, geological-like crystal forms, the exact nature of which depended on the environment in which fossilization occurred. These data strongly suggest that it is impossible to extrapolate the age or native state of fossil bones through such archeological techniques as carbon dating. The fossil bone work was done in collaboration with A. Hassan at Southern Methodist University.

The future plans of the section involve no fundamental change in direction. Most future projects will be continuations of current research efforts. Certain projects, however, will be intensified. Among the synthetic calcium phosphate studies, major emphasis will be placed on the interaction of aqueous solutions of calcium and phosphate with apatitic substrates. Particular attention will be given to elucidating the different pathways by which new material is accreted onto apatitic surfaces under varying conditions of solution supersaturation. The purpose of this study will be to establish the fundamental physicochemical mechanisms by which enamel apatite responds to changes in oral fluid environment.

Spectroscopic studies on mineral-matrix binding will be given increased emphasis during the coming year. Collagen-mineral, phosphoprotein-mineral, and proteoglycan-mineral complexes will be examined. Increased effort will also be given to the quantitative evaluation of the x-ray diffraction properties of hard tissue mineral. Particular attention will be directed to toxicological, hormonal, and pharmacological effects on the mineral quality of normal and chronically uremic bone tissue.

Summary Report of the Structural Interactions Section
Laboratory of Biological Structure
National Institute of Dental Research

The basic interests of the Structural Interactions Section continue to center on plaque deposits and may be grouped into three general areas of effort: (1) predominant organisms; (2) their polysaccharide by-products; and (3), development of methods for control of plaque deposition on both hard and soft tissue. Knowledge of types of microorganisms comprising plaque is essential. Our efforts in this area are particularly well documented by our continuing studies aimed at evaluating the potential usefulness of fluorescent antibody techniques (FAB) and radioimmune assays for rapid identification and quantitation of specific microorganisms in plaque. The importance of both soluble and insoluble bacterial polysaccharides as mediators of adherence of oral microorganisms to tissues cannot be overemphasized. New methods of study are currently in use to determine if differences exist between these and other polysaccharides which may give some insight into the mode of attachment of disease-causing organisms.

The development of methods for the rapid detection of oral actinomyces and actinomycete-like bacteria remains a prime undertaking of this section. In collaboration with Dr. Lucille George and Dr. William Kaplan of CDC, fluorescent antibody conjugates are being developed and evaluated for the various serotypes of Actinomyces viscosus, Actinomyces naeslundii and Actinomyces israelii.

In collaboration with Dr. L. A. Thomson of the Caries Prevention and Research Branch, an assessment of the excitation light source for fluorescent microscopy was made. Lamps studied were the 75, 150, and 450 watt Xenon lamps, the 100 watt halogen lamp and the 100 and 200 watt mercury lamps. In conjunction with a Ploem vertical light illuminator the Xenon 450 watt lamp provided the most intense fluorescein fluorescence. This allowed greater dilutions of conjugate to be made (2-4 x) which results in substantial advantages in studies where original FA titers are low or are of limited supply.

Previous studies have shown that serum antibodies to plaque organisms are found in patients with periodontal disease. In a collaborative study with Dr. N.A. Cummings of the Laboratory of Oral Medicine, IgG antibodies specific for A. viscosus but not A. naeslundii or A. israelii were found in the serum and gingival extracts of a patient with juvenile periodontitis. This data strengthens the evidence for the potential importance of A. viscosus in periodontal inflammation and a systemic immune reaction to plaque antigen. Since the gingivae were grossly infiltrated by plasma cells, these observations also raise the question of local synthesis of antiplaque antibody.

Investigations utilizing the plant lectin, Concanavalin A (Con A), have demonstrated that this compound is a useful tool in studies concerning the molecular structure of various bacterial polysaccharides, since it binds to glucose, fructose or mannose moieties. These saccharides constitute a substantial portion of many of the polysaccharides produced by oral organisms and appear to be of importance in the etiology of caries and periodontal disease. We have initiated studies using Con A to determine if some common denominator exists between polysaccharides which can be related to the disease process.

When Con A was reacted with numerous strains of oral streptococci and actinomycetes grown in either sucrose, glucose, fructose, or maltose, significantly more Con A was bound by cells grown in sucrose than in any of the other sugars. Other parameters affecting this reaction were studied in detail so that standard conditions could be defined.

To evaluate possible differences between surface polysaccharides of plaque and non-plaque forming organisms we chose Streptococcus mutans C67-1 which formed plaque and was caries-active. The other organism was C67-25, a mutant of C67-1, which did not form plaque or caries. When Con A was reacted with these organisms grown in sucrose, it was observed that C67-1 bound approximately 50% more Con A than C67-25. The amount bound by the mutant in each of four different sugars was similar to that bound by the parent strain in glucose, fructose or maltose. This clearly demonstrates that a chemical difference exists in the polysaccharide component of the cell surface of the parent (caries-active) and mutant strain (caries-inactive). This same type of relationship was found to exist in several concentrations of sucrose, suggesting that the same spectrum of polysaccharide-forming enzymes are present on the cell surface regardless of substrate concentration.

When sucrose- or glucose-grown cells of both the parent and mutant strain were treated with KOH, the sucrose-grown cells of the parent lost their additional interaction with Con A. The parent strain grown in sucrose and treated with KOH interacted with Con A to the same degree as if it had been grown in glucose alone, suggesting that the cell-bound product from sucrose was more soluble in alkali.

Generally the interaction of Con A with strains of Str. mutans and actinomycetes revealed that the streptococci bound considerably more Con A when grown in sucrose than when grown in glucose. Actinomycetes on the other hand bound almost identical amounts of Con A regardless of whether they were grown in glucose or sucrose. It is possible that these data reflect the plaque-forming potential of these organisms, since streptococci will form plaque only from sucrose while actinomycetes will do so from a wide variety of carbohydrates.

When the interaction of Con A with various isolated bacterial polysaccharides was investigated, it was found that the polysaccharides isolated from whole cells using either 45% or 70% ETOH were essentially identical as regards Con A binding.

When the effect of concentration of polysaccharide on the binding of Con A was investigated, it was shown that the polysaccharides isolated from three strains of Str. Mutans had similar reaction rates throughout the concentrations tested. The two actinomycete polysaccharides tested had identical reaction rates which were vastly different from those of the streptococcal polysaccharides. The interaction is much faster with the actinomycete polysaccharide, and probably is a reflection of more available binding sites, i.e. a different polysaccharide.

Work is presently continuing with polysaccharides produced by various oral organisms. Since results obtained thus far with polysaccharides produced by whole cells reflects the interaction of several polysaccharides, attempts are now being made to find methods to isolate individual molecular species.

Investigation of each of the above-mentioned areas will be continued and intensified during the coming year. Studies concerning the identification of oral actinomycetes are presently at a stage where several potentially meaningful approaches utilizing the FAB technique are being discussed. Studies on the polysaccharides of oral organisms are being extended to include pilot programs designed to determine how soluble and insoluble products are involved in plaque matrix formation.

Summary Report of the Laboratory of Microbiology and Immunology
National Institute of Dental Research

With the reorganization of certain intramural programs at NIDR during FY 1974, all of the existing microbiological components of the Institute were structured administratively under the Laboratory of Microbiology and Immunology. A coordinated program in oral bacteriology will allow for more innovative approaches to problems associated with dento-bacterial plaque, which is now fully appreciated as being the principal etiologic factor in both periodontal diseases and dental caries. Because of the diversity of bacterial species etiologically related to these disease processes, research in oral microbiology which ultimately will be applicable to prevention and treatment of oral disease must be approached in a manner that is unique to the programs and setting of this Institute at NIH. The individuals working in microbiology are presently involved in three broad categories of research: (1) physiological and metabolic studies on oral bacteria, (2) mechanisms of microbial pathogenicity and mechanisms of and factors controlling microbial adherence to hard and soft dental tissues and (3) studies on the ecology, taxonomy and phylogenetic relationships of oral bacteria. These programs are, therefore, directly concerned with basic mechanisms of experimental and clinical dental caries and periodontal diseases.

This laboratory has always contemplated the shifting fashions in dental research and has responded to meet the research needs of the day. When it was recognized that the virology component of this laboratory should be expanded into the present-day Laboratory of Oral Medicine, it strongly advocated the creation of this free standing unit. In similar fashion, it is anticipated that the present Laboratory of Microbiology and Immunology will, at a suitable time, give birth to a free standing unit in oral microbiology once program areas are more clearly defined in terms of the total mission of the NIDR.

During recent years, a surge of experimental evidence has accumulated which points to a number of immunopathological mechanisms underlying the tissue destruction observed in oral inflammatory diseases. During the past year, the immunology component of this laboratory was strengthened by the establishment of a clinical immunology section in the clinical investigations laboratories of NIDR. It is anticipated that our newer immunological techniques and approaches to problems in oral biology can now be applied at the clinical level with access to human patient material. In addition, the section will pursue fundamental studies on the role of allergic inflammatory reactions in the pathogenesis of oral mucosal diseases.

One of the continuing responsibilities of any Laboratory Chief is to maintain a solid base of creative scientists. Recent cutbacks in personnel and restrictions on hiring have been a handicap in developing fully our programs, but this deficiency has been partially overcome by the attraction of guest workers, Fogarty visiting fellows and postdoctoral fellows to this Laboratory. It is a tribute to our program leaders who have labored successfully in attracting talented individuals who seek further experience and training in

oral microbiology and immunology. At the same time these young scientists are contributing in a major way to our ongoing programs.

For summarization purposes, the major activities of the laboratory are presented according to section designations. It should be appreciated that these investigations have entailed numerous collaborative and contracted projects with other laboratories at NIH and outside institutions.

Summary Report of the Microbial Physiology Section
Laboratory of Microbiology and Immunology
National Institute of Dental Research

The Microbial Physiology Section as originally formed in 1968 had the broad-based mission of studying diverse physiological phenomena of microorganisms, and of attempting to explain these phenomena in precise molecular terms. This endeavor was most successful over a period of several years. It led to the discovery of several fundamental metabolic principles that proved to be of general biological significance, to numerous contributions in the area of systematic microbiology, and to the development of an innovative approach to the study of the evolution and phylogenetic relatedness among the lactic acid bacteria. Over the past few years, this more or less undifferentiated approach to the study of oral microbiology has evolved systematically into a more structured program, with individual research projects that relate more directly to basic aspects of two of the most prevalent and costly afflictions of man, periodontal disease and dental caries. A major objective of this program is to delineate fundamental principles that will serve as a knowledge base for formulating rational approaches to the control of these pathological states, both of which result from complex interactions between the oral microflora and the host.

The past year's research accomplishments of the Section will be summarized under three broad categorical areas: 1) taxonomy and ecology of microorganisms; 2) mechanisms by which microorganisms successfully colonize the diverse oral econiches; and 3) microbial metabolism and its regulation. It is pertinent to emphasize that due to various personnel and budgetary restrictions the number of research projects under investigation in each of these categorical areas has necessarily been limited.

Taxonomy and Ecology of Microorganisms: An obvious prerequisite for studying microorganisms that comprise any ecosystem is the establishment of reliable means for their identification and characterization. A major effort relating to this problem has been a complete updating of the comparative descriptions of taxonomic groups of gram positive, non-sporeforming rods. This extensive undertaking has now been completed. A series of manuscripts describing relationships of a number of families, genera, and the species included therein will appear in the 8th edition of Bergey's Manual of Determinative Microbiology (1-17).

Complementing these systematic studies, is our continuing effort to define the phylogenetic relationships among the lactic acid bacteria, and our attempts to resolve the evolutionary processes that lead to the ability of certain streptococci and lactobacilli to colonize various econiches within the oral cavity. A phylogenetic map of the homofermentative lactic acid bacteria, based on the structural homology of the enzyme fructose diphosphate aldolase, was assembled and described last year using the enzyme from Streptococcus faecalis as the reference point (18). The map initially included species belonging to the following genera; Streptococcus, Lactobacillus, Pediococcus and Microbacterium. The utility of this technique of natural classification went beyond simply relating one species of organism to another; it also aided in the speciation of phenotypically similar, but genotypically diverse strains of streptococci and lactobacilli. The initially derived relatedness group has recently been expanded to include at least four species of Acholoplasma (Mycoplasmatales) as well as a number of obligately anaerobic Gram positive

rods from the genera Butyribacterium, Eubacterium and Propionibacterium.

Since the results reported above were obtained with a single reference point, it was necessary to corroborate the data with a second reference aldolase. To this end, the enzyme from Pediococcus cerevisiae was purified and used as an antigen to produce specific antisera. The data obtained thus far corroborate, in general, the antigenic groupings and order of relatedness observed with the anti-streptococcal aldolase serum, however, the map now requires some modification. The pediococci are more closely related to the lactobacilli than to their morphological counter parts, the streptococci. Use of the new antisera has added a new genus to the list of near-relations, namely, Aerococcus. While the aldolases of these organisms do not react with anti-streptococcal aldolase, they do react with anti-pediococcal aldolase.

The molecular evolution of the aldolases themselves has also been studied, and molecular weight differences appear to reflect substantive changes in the size and arrangement of a common subunit. It now appears that an alteration in the aldolase gene occurred concommitant with the evolution of the streptococci as a distant group. In addition, the characterization of a second aldolase in L. casei, which happens to be a class I aldolase or mammalian type (19), may be of importance in defining the course of evolution of these organisms. Such an enzyme occurs very rarely among prokaryotes and is found only in this one species of Lactobacillus.

These studies oriented toward establishing a more comprehensive understanding of oral ecology will be continued. The comparison of lactic acid bacteria aldolases with both the anti-streptococcal aldolase sera and anti-streptococcal aldolase sera and anti-pediococcal aldolase sera will be completed. In addition, a complete biochemical study of the class I (Schiff-base) aldolase of L. casei will be undertaken with the objective of ascertaining whether this organism is a "living relic" within the Lactobacilliaceae. Finally, a second enzyme, glyceraldehyde-3-P dehydrogenase is being purified from several lactic acid bacteria to provide a completely independent means of determining the accuracy of the aldolase map and enlarging it. These antisera will also be used to clarify the species S. mitis (mitior) and to better circumscribe S. sanguis and S. salivarius.

Since glyceraldehyde-3-P dehydrogenase is present in relatively high levels within the lactic acid bacteria and is easily purified, sufficient antiserum could be prepared to permit an epidemiological survey of the streptococci in the oral environment of patients in the Clinical Center. One objective of such a survey would be to learn whether the four biotypes of S. mutans are restricted or ubiquitous in individuals on the basis of age, state of health and medical care.

Mechanisms of Microbial Colonization of the Oral Cavity. It is widely accepted that extracellular glucans produced by S. mutans are involved both in the adhesive interactions among these organisms and in their colonization of the tooth surface. The mechanisms by which these extracellular polysaccharides are synthesized, therefore, is being actively studied.

The constitutive extracellular glucan synthesizing system (glucosyltransferase) of S.mutans 6715 has been purified 400-fold from cell-free growth medium. The enzyme is a glycoprotein which contains up to 78% carbohydrate of as yet unknown composition. The carbohydrate moiety appears to be required for catalytic activity, since its removal by treatment of the glucosyltransferase with dextranase results in a complete loss of activity (20). The purified preparation has recently been further fractionated into two major

enzyme components (21). One component produces primarily water insoluble glucans from sucrose and is designated as insoluble product enzyme (IPE). The other component produces water soluble glucans from sucrose and is designated as soluble product enzyme (SPE). The two components have been shown to be immunologically different when tested with antiserum prepared against whole cells of S. mutans 6715. An equal mixture of IPE and SPE synthesize essentially all insoluble product from sucrose; twice that amount produced by IPE alone. This fact, considered with the observation that very little water soluble glucan can be detected during the initial linear phase of the reaction, suggests that any soluble product synthesized within this time may be incorporated into the insoluble product. Soluble carbohydrate polymers do appear, however, after prolonged incubation of IPE and SPE with sucrose. This may be due to the removal of IPE by the insoluble glucans produced, and/or to the inhibition of insoluble glucan synthesis by increasing concentrations of fructose, the second product of the glucosyltransferase catalyzed reaction. It has been shown that fructose does indeed inhibit the synthesis of insoluble glucan by the purified, unfractionated glucosyltransferase.

The glucans synthesized from sucrose by IPE or SPE differ in aspects other than their relative solubility in water. Treatment of the SPE product with fungal dexrranase converts 100% of the original material into carbohydrates soluble in 75% ethanol. Similar treatment of the IPE product, on the other hand, converts only 65% of the original material into carbohydrates that are soluble in 75% ethanol. This observation suggests the presence of a larger percentage of α-1,6 linkages in the water soluble glucans and more α-1,3 (or other) linkages in the water insoluble product.

The two major components of the purified glucosyltransferase (IPE and SPE) have also been analyzed by polyacrylamide gel electrophoresis in an effort to gain further insight into their enzymatic composition. IPE shows 8 different protein bands, each of which produces a water insoluble product from sucrose. All of these bands have approximately the same molecular weight (150,000), but differ with respect to their net charges. SPE shows only 2 protein bands, both of which synthesize water soluble glucans from sucrose. The major band has an approximate molecular weight of 190,000, while the minor band has a molecular weight of 110,000. Both of these bands have similar net charges.

The available data indicate the highly complex nature of the glucan synthesizing system in S. mutans. Future studies will be directed toward a more complete characterization of this multicomponent enzyme system and toward the accumulation of information that will lead to a better understanding of its role in cell adhesion and colonization of the tooth surface.

Microbial Metabolism and its Regulation. Metabolism, reduced to its most basic terms, is the process of transforming a series of relatively simple compounds into the complex structural and functional molecules essential for maintenance and reproduction of the cell. Clearly, however, no carbon source can fulfill any of the microbial cell's needs unless it can be brought into the cell and mobilized to participate in one or more of the existing metabolic pathways. This initial event in the process of cellular metabolism is being studied in S. mutans.

The widespread use of mannitol and sorbitol fermentative ability as a phenotypic characteristic for distinguishing S. mutans from other oral streptococci prompted an investigation into the mechanism of hexitol transport. These studies have shown that the transport of mannitol by S. mutans 6715 is mediated by at least two enzymatic reactions. A phosphate group is transferred from phosphoenolpyruvate to a heat-stable protein (HPr) by a constitutive enzyme (I). The heat-stable component has been partially purified from extracts of glucose-grown cells and shown to have a molecular weight of greater than 1,000 but less than 10,000. The phosphorylated HPr then serves as a phosphate donor for forming mannitol-1-phosphate (MIP) by a membrane-bound enzyme complex (II).

At least one component of the mannitol phosphotransferase system is inducible (22). Crude cell extracts prepared from S. mutans 6715 grown on sucrose, fructose, lactose, galactose, or mannose contained less than 10% of the MIP generating activity found in extracts of mannitol-grown cells. Evidence for which of the components was inducible was obtained by fractionating crude cell extracts by ultracentrifugation (100,000 x g). In E. coli, enzyme I and HPr are present in the soluble fraction and the enzyme II complex occurs in the pellet (membrane and/or wall fraction). Soluble and pellet fractions were prepared from both glucose- and mannitol-grown cells of S. mutans 6715. Neither fraction obtained from glucose-grown cells nor a combination of the two fractions contained significant MIP generating activity. The mannitol-derived pellet was also devoid of activity. When the glucose-derived soluble fraction was mixed with the mannitol-derived pellet, however, full MIP generating activity was restored. It appears, therefore, that the inducible component is the membrane (and/or cell wall)-bound enzyme II complex.

The S. mutans 6715 phosphotransferase system seems to be very similar or identical to that reported previously for E. coli (23) and a number of other facultative anaerobes. However, certain subtle but perhaps important differences have been found. For example, Ca^{++} is a potent inhibitor of the E. coli phosphotransferase system but this cation can replace Mg^{++} in the S. mutans MIP generating system. Moreover, Zn^{++} can partially replace Mg^{++} in the E. coli system but is a strong inhibitor of the S.mutans mannitol phosphotransferase system. The role of these divalent cations in vivo remains unresolved, but the utilization of Ca^{++} by S. mutans may reflect adaptation of this organism to its environment. It should be noted that the mannitol phosphotransferase system described here for S. mutans 6715 is not unique to this particular strain. It has also been demonstrated in crude extracts from mannitol-grown cells of strains AHT, BHT, LM-7 and C-67-1.

Recently, several mutants of S. mutans have been selected for their ability to grow on either glucose or galactose but not on mannitol. Two different classes of mannitol-deficient mutants have been observed to date. Growth of one class is unaffected by the presence of mannitol in a complex medium containing glucose. The addition of mannitol to cells of the second class growing in complex medium containing glucose, however, inhibited growth. It is anticipated that further studies with these sensitive and resistant mannitol-deficient mutants will provide insight into the biochemical basis of the growth inhibitory effect and possibly provide additional information on the physiological mechanism of the transport and catabolism of carbohydrates.

Another ongoing project within the Section deals with mechanisms by which the biochemical activities of the microbial cell are regulated. Past studies demonstrated that glucose-grown cells of Streptococcus faecalis possessed the enzymes of the oxidative portion of the hexose-monophosphate pathway as well as all of the enzymes of the Embden-Meyerhof pathway. This organism, therefore, has the potential to metabolize glucose by either of these two pathways. It was established from work in other laboratories, however, that virtually all of the glucose degraded by S. faecalis proceeded through the Embden-Meyerhof pathway with the stoichiometric accumulation of lactate. In searching for a biochemical explanation for this preferential use of the Embden-Meyerhof pathway, it was found that the glycolytic intermediate fructose-1,6-diphosphate (FDP) acts as a modifier for a key enzyme from each of the pathways. This compound is a specific and absolutely required activator for the lactate dehydrogenase (LDH), and a potent and specific inhibitor of the 6-phosphogluconate dehydrogenase dehydrogenase (6PGD) (24). More recently, another regulatory site in the glycolytic pathway has been identified. This organism contains two pyruvate kinases, which have been isolated and separated by molecular sieving techniques (25). One enzyme (molecular weight of 200,000) has a high K_m for its substrate (phosphoenolypyruvate) and its activity is unaffected by FDP. The other enzyme (molecular weight of 100,000) has a low K_m for its substrate and is almost completely dependent upon FDP for catalytic activity. The physiological role of these two forms of pyruvate kinase is currently under investigation.

Utilizing the information accumulated from the work with S. faecalis as a base, a series of comparative studies have been undertaken with various members of the oral microbiota. All biotypes of S. mutans have an FDP-dependent LDH, but certain kinetic properties of the enzyme differ from one biotype to the next. None of the S. mutans biotypes possess any of the oxidative enzymes of the hexose-monophosphate pathway. A. viscosus T-6 and M-100 and A. naeslandi do have both oxidative enzymes of the hexose-monophosphate pathway and the 6PGD from each of these organisms is inhibited specifically by FDP. The LDH from these actinomycetes is also activated by FDP, but in a manner quite distinct from that found in either S. faecalis or the various S. mutans biotypes. The enzyme is totally unresponsive to FDP at saturating concentrations of pyruvate. At rate limiting concentrations of pyruvate, however, the modulating ligand exerts a dramatic stimulatory effect.

It is anticipated that these comparative studies will be continued with a view toward 1) establishing general principles of cellular control processes, and 2) possibly uncovering unique aspects of cellular metabolism in the oral organisms that may help define their pathogenicity in specific biochemical terms.

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Summary Report of the Cellular Immunology Section
Laboratory of Microbiology and Immunology
National Institute of Dental Research

It is the mission of the Cellular Immunology Section to investigate the role of cellular reactions, interactions and cell products in immunological reactions. The mechanisms of activation and inactivation of host defense against disease is dependent on immunological reactions which are mediated by lymphocytes and accessory inflammatory leucocytes such as macrophages, neutrophiles and basophiles. Investigations of the regulatory relationships between these cells should lead to an understanding of the factors contributing to inflammation and hopefully also to the development of therapeutic means of modifying these reactions.

There are two major subpopulations of lymphocytes with distinct functions that are responsible for different types of immunological reactions. Normally, these two types of immunoreactive populations also serve to regulate the magnitude of the inflammatory responses, but they have been found to be imbalanced in a variety of diseases. The lymphocyte populations consist of bone marrow-derived (B) lymphocytes that have surface immunoglobulin receptors, differentiate into antibody producing cells and are therefore responsible for humoral types of immunological reactions. In contrast, thymic-derived (T) cells do not have any readily detectible surface immunoglobulin and are known to produce a variety of nonspecific mediators of inflammation involved in cell-mediated immunological reactions, such as delayed hypersensitivity and homograft rejection. B cell antibody products have been found to modulate the degree of reactivity of T cells, whereas T cells are thought to make factors that enhance or inhibit antibody production by B cells.

During the past year the ongoing investigations in our section have focussed on elucidating further the functions and interactions of these two classes of lymphocytes. We have employed a variety of tissue culture assays of lymphocyte proliferation, mediator and antibody production and studied this problem in various animal models such as guinea pigs, mice, chickens and verified some of these principles by human investigations.

The somewhat unexpected observation was made by Dr. L. Altman (in collaboration with Dr. B. Mackler) that under certain circumstances 97 $\pm$ 2% pure human peripheral blood B cells as well as 97 $\pm$ 2% pure T cells would not only manifest significant proliferative responses to several T cell mitogens and antigens, but also would elaborate considerable amounts of a mediator, namely, monocyte chemotactic factor (MNL CTX). It was observed that B cells which were rosetted with EAC (sheep red blood cells SRBC, coated with 19S anti-SRBC and mouse complement) and fractionated on Ficoll-Hypaque gradients were stimulated by the EAC to make MNL CTX, whereas EAC failed to stimulate T cells. Furthermore, removal of the EAC with anti-C3 reversed this phenomenon. In addition, Dr. M. Iverson in parallel studies observed that EAC would also activate a small but significant number of mouse (and human) B cells to make antibodies against SRBC as well as some other antigens. Thus,

EAC were found to polyclonally activate B cells to make antibodies, to produce MNL CTX and to lower the threshold for their proliferative response to T cell mitogens. Subsequently, Dr. S. Wahl has extended these findings in guinea pigs by demonstrating that not only EAC, but LPS, aggregated immunoglobulin, antigen-antibody complexes and anti-immunoglobulins all can activate B lymphocytes to make MNL CTX. These observations thus establish the principle that many different types of stimulants which interact and cross-bridge various cell surface receptors on B cells also activate the cells to make a mediator in the absence of proliferation.

Dr. M. Wilton also came to the conclusion that guinea pig B cells make another mediator that activates macrophages (MAF). He observed that lipopolysaccharide endotoxin (LPS), a B cell mitogen, could activate macrophages to incorporate C^{14} glucosamine, only when they were in the presence of B cells and not T cells. In fact, culture supernatants of LPS-activated, purified B cells also activated macrophages. The importance of these observations is reinforced by collaborative studies of Drs. S. and L. Wahl, S. Mergenhagen and G. Martin showing that LPS-activated macrophages also make collagenase. Therefore the previously held conclusion that lymphocyte mediators are exclusively T cell products and provide the only cause for inflammatory reactions in cell mediated immunity must be modified. Thus, B cells may directly contribute to all types of inflammatory reactions through the production of mediators.

These observations were also applied to investigate the problem of periodontal disease in which inflamed tissues are rich in plasma cells of the B cell type as well as in chronic inflammatory mononuclear cells. It was observed by L. Altman and B. Mackler that antigens present in pooled plaque deposits could stimulate B as well as T lymphocytes from patients with periodontitis (but not normal subjects) to proliferate and to produce MNL CTX. Thus, both of these classes of lymphocytes actively contribute to the inflammatory response in periodontal disease. Since LPS stimulated human B cells to only a limited degree, other bacterial antigens are presumably responsible for the stimulating effect of plaque. However, Dr. W. Radentz and Dr. J. Oppenheim are finding that mitogenic stimulants are present in some of our foods such as corn and nuts. Since they also activate lymphocytes to proliferate and to produce MNL CTX, it is conceivable that if such food mitogens penetrate the gingival tissues, they may also contribute directly to gingival inflammation.

Drs. D. Rosenstreich and J. Oppenheim are investigating the mechanism by which macrophages enhance lymphocyte reactivity to antigens and T cell mitogens. They have found that LPS activation of guinea pig B cells is inhibited rather than enhanced by macrophages. Furthermore, the antigen induced proliferative response of purified T cells can be shown to be dependent on macrophages, whereas proliferative responses of purified B cells to antigens are not increased in the presence of macrophages. However, when B cells are in the presence of T cells, the lymphoproliferative reactions of T and consequently B cells to antigens are both increased in the presence of macrophages. This suggests that macrophages, by activating T cells, in turn indirectly facilitate T-B collaboration. In addition, Dr. S. Wahl has observed that antigen-induced production of MNL CTX by guinea pig lymphocytes is dependent upon the presence of macrophages. Finally, similar conclusions have been reached by Dr. J. Horton and collaborators who observed that only

in the presence of macrophages can PHA-induced human lymphocytes make a factor which resorbs bone (OAF). The prediction that OAF is therefore made by T cells under these circumstances is in the process of being tested. The observation of Drs. J. Oppenheim, with L. Raisz and coworkers, that long-term tissue culture lymphoid cell lines of the B cell type also make OAF suggests that when appropriately activated normal B lymphocytes may also make OAF.

Dr. D. Rosenstreich is investigating the cell type responsible for another important immunological effector phenomenon, namely, antibody-dependent cell mediated cytotoxic effects on target cells. He finds that macrophages coated with antibody can be potent killer cells, but there is also a weakly adherent nonphagocytic cell that can be cytotoxic in the presence of antibodies. These studies may elucidate mechanisms by which cells may directly lyse targets such as invading bacteria or immunogenic tumor cells.

Finally, Drs. D. Rosenstreich and S. Mergenhagen in collaboration with Dr. A. Nowotny are pursuing their studies of mechanism of B cell activation by the lipid A component of LPS. They have found that certain synthetic nontoxic glycolipids can mimic the mitogenicity of Lipid A. Furthermore, they find the LPS response to be under genetic control in mice. This principle may be applicable to understanding apparently idiosyncractic disease susceptibilities in man, including periodontal disease.

The cellular immunology section will shortly be losing the contributions of Dr. M. Iverson who will be leaving us to join the staff of Stanford University. In his stead, Dr. John Farrar, a Senior Staff Fellow, will be transferring to us from the NICHD Gerontology unit. His interest in mediators that facilitate T-B cell cooperation complements our activities and should strengthen our research activities in this area during fiscal year 1975.

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Summary Report of the Clinical Immunology Section
Laboratory of Microbiology and Immunology
National Institute of Dental Research

The Clinical Immunology Section was created in April 1973 to integrate basic with clinical immunological studies. The aim of this section is to define humoral and cellular mechanisms of immunological tissue injury. For this purpose, we are exploring cellular and humoral mechanisms in animal model systems of immune injury, and their possible manipulation, while, at the same time applying similar techniques to clinical studies.

The cellular mechanisms involved in autoimmune reactions are under study by Dr. T. Chused. Patients with the autoimmune disease; Sjogren's syndrome, develop widespread lymphoid infiltrates in many organs. A large proportion of such lymphocytes in these patient were identified as B cells, as demonstrated by the adherence of complement bearing erythrocytes. Investigations are currently under way to determine a suitable method to distinguish T cells in tissue infiltrates, with the view of using both techniques to study infiltrates in oral biopsy sections. In collaboration with Dr. R. Genco (State U. N.Y., Buffalo) biopsy specimens from an experimental primate model of periodontal disease are also being examined for T and B cell infiltrates.

New Zealand mice are utilized as an experimental model for autoimmune disease. Studies are attempting to dissect and define the respective roles of T and B cells in this disease process. The graft versus host reaction (GVH) was used as a functional test for T cells. The GVH activity of NZB/W spleen cells rises from 1 to 6 months of age and then falls rapidly. Thymocytes from 1 month old mice suppress the GVH activity of the spleen cells from 6 month old mice. In contrast, normal mouse strains show stable GVH reactivity and no suppression of the syngeneic spleen cell GVH by thymocytes. These experiments have been interpreted to indicate that NZB/W mice lose a thymic derived suppressor or regulatory cell as they age, and this coincides temporally with the development of autoimmune phenomena. Similar results have been obtained in a study of B/W and normal spleen cell response to the lymphoid tumor EL-4 both in vivo and in vitro. In collaboration with Dr. Holger Kirchner (NCI) suppressor phenomena are being studied in a murine tumor system. Spleens from mice with an MSV-induced tumor contain a population of suppressor cells that preferentially inhibit T cell function.

Experimental studies are utilizing the plant lectin, Concanavalin A (Con A) to investigate the mechanisms involved in the activation of basophils to release histamine and other mediators of inflammation. Initial investigations revealed that Con A can release histamine from mast cells or basophils of a number of species. The mechanism has been investigated in detail in humans; there was wide variation in the response of the basophils of different individuals. The response has great similarity to antigen activation of basophils in its biochemical and metabolic aspects. The Con A binds to pyranosyl sugar residues on the cell membranes. Investigations are attempting to determine whether the Con A induced basophil reaction is due to the lectin binding IgE on the cell membrane.

The nature of the compounds which can activate basophils for histamine release is under study. A series of bivalent haptens with the general formula $R\text{-}NH\text{-}(CH_2)_n\text{-}NH\text{-}R'$ were used to test for histamine release from basophils. Monovalent hapten (R'=H) were inactive whereas the bivalent haptens (R=R') were active even when n was as small as 3. The most active compounds were n=6-9 and these were as active as a multivalent compound. Similarly a compound which has two different haptens at R' and R is active only on basophils which have been obtained from animals immunized with both haptens. These experiments are interpreted to indicate that histamine release and cell activation is due to simple bridging between two molecules on the cell surface with the formation of a dimer.

The role of complement (C) and platelet interaction in mechanisms of inflammation is being investigated. Prior studies have shown that the rabbit deficient in C6 is a model for studies in the interrelationship of the C and clotting systems. The C6 deficient rabbits have a clotting abnormality which is due to a defective platelet release reaction. In these rabbits endotoxin and immune complexes cannot activate the release of platelet factor 3 and clotting is therefore prolonged. Similarly, a factor is released from rabbit basophils during antigen-antibody induced reactions which brings about platelet aggregation. This reaction requires no complement or serum factors. It would function as an amplification system for immunological injury reactions. Investigations are under way to determine whether a similar reaction occurs following immunologic release reactions of basophils from human patients.

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Summary Report of the Humoral Immunity Section
Laboratory of Microbiology and Immunology
National Institute of Dental Research

The Humoral Immunity Section investigates the role of mediators of inflammation generated either via the complement system or from activated lymphocytes. Elucidation of the mechanism by which these biologically active molecules are produced will provide a basis for the therapeutic manipulation of the inflammatory response.

The contribution of the classical complement system to the induction of inflammation has been and remains the subject of extensive investigation. Thus, it participates in the production of increased vascular permeability, contraction of smooth muscle, release of vasoactive amines, destruction of cells and the directed migration of inflammatory cells. Recently, an alternate pathway of complement activation has been described and its contribution to the inflammatory state requires further study. Immunoglobulin activation of the classical complement pathway with resultant production of anaphylatoxic or chemotactic fragments has been well documented. However, the influence of various classes of antibodies on activation of the alternate complement pathway remains to be delineated.

Generation of factors contributing to the inflammatory response is not a unique property of the complement system. Lymphocytes are also capable of elaborating agents which initiate or modulate the processes involved in inflammatory reactions. After appropriate stimulation, lymphocytes synthesize and secrete substances with various biological functions, including chemotaxis of inflammatory cells and bone resorption. Since both the humoral and cellular responses are involved in immune pathology, the interaction of these two immune systems may be crucial in the modulation of the overall effects observed.

Drs. A. Sandberg and S. Mergenhagen in collaboration with Dr. L. Raisz (University Rochester School of Medicine) are investigating the role of complement in bone resorption. Fetal rat bones in organ cultures are resorbed in the presence of complement sufficient serum. The effect is abrogated if heated (complement insufficient) serum or serum from rabbits genetically deficient in the sixth component (C6) of complement is incorporated into the culture medium. The addition of functionally purified C6 to the C6 deficient serum restores resorptive activity. This effect is mediated by prostaglandins, as demonstrated by the finding that prostaglandin synthesis is markedly enhanced in the bone cultures containing complement. Indomethacin, an inhibitor of prostaglandin synthetase, obliterates both the appearance of prostaglandins in the culture media and the bone resorption. Immune activation of complement at a cell surface initiates this activity, in that resorption is markedly enhanced by the addition of tissue specific immunoglobulins, whereas non-tissue related immune complexes are ineffective.

Drs. A. Sandberg and S. Mergenhagen are continuing studies designed to determine the role of antibodies in the activation of the two complement pathways by endotoxic lipopolysaccharides. Sera depleted of immunoglobulins

no longer support complement activation by these agents, and antibody containing preparations restore the activity. The possible concomitant depletion of additional components of the alternate complement pathway is currently the subject of extensive investigation.

The immunochemical characterization of a previously undescribed 7S guinea pig immunoglobulin class has been initiated by Dr. A. Sandberg. Separation of this class of antibody from the two defined classes of guinea pig immunoglobulins (gamma-1 and gamma-2) has been achieved by ion exchange chromatography. These antibodies are detected primarily after immunization with particulate antigens such as sheep erythrocytes, and are effective in the complement-dependent destruction of red blood cells. Their other biological properties remain to be explored.

Antigenic structure may in part determine which complement pathway is activated. Studies by Drs. A. Sandberg and R. Siraganian have demonstrated that guinea pig immunoglobulins which activate the classical complement pathway form complement-reactive complexes with small divalent haptens of defined size. None of these haptens are capable of forming complement reactive complexes with immunoglobulins which activate only the alternate complement pathway.

Dr. Sandberg has collaborated with Dr. Siraganian in further studies of the role of the alternate pathway in the induction of platelet lysis. Agents considered to be activators of the alternate complement pathway are as effective as activators of the classical pathway in the release of histamine and coagulation fractors from platelets.

Drs. Sandberg and Mergenhagen in collaboration with Dr. A. Notkins and Dr. C. Daniels (Duke University School of Medicine) are continuing their studies concerning the role of the alternate pathway in protection against viral infection. Whereas immune activation of the classical pathway is markedly efficient in inducing lysis of viral infected cells, the alternate pathway appears to be only minimally effective. Current studies explore the relative contribution of both pathways to viral neutralization.

Dr. L. Altman has continued his studies of chemotactic lymphokine synthesis and monocyte chemotaxis in human disease. Extensive studies in children with Wiskott-Aldrich syndrome, a lethal immunodeficiency disease, and patients with Hodgkin's disease and non-Hodgkin's lymphoma are in progress. In addition, patients with chronic lymphatic leukemia, a disease characterized by abnormal B lymphocyte proliferation, and Sézary's syndrome, a T lymphocyte disorder, are being studied. A second major area of endeavor has been the study of chemotactic lymphokine synthesis by purified human T and B lymphocytes. Recent developments have allowed the separation of lymphocyte subpopulations from human peripheral blood, and these techniques have been utilized to study the mechanism of activation of T and B lymphocytes. These studies have surprisingly revealed that B lymphocytes, previously thought to be solely Ab producing cells, also produce lymphokines.

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Dr. S. Wahl joined the Humoral Immunity Section in March 1974 and in collaboration with Dr. A. Sandberg is now initiating studies concerning the interactions of cellular and humoral immunity.

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Report of the Laboratory of Oral Medicine
National Institute of Dental Research
Summary Statement

This is the first annual report of the Laboratory of Oral Medicine (LOM). LOM was created in the spring of 1973 to study diseases of the soft tissue of the oral cavity with emphasis on: 1) herpes simplex virus; 2) aphthous ulcers and other dermatologic disorders; 3) exocrine and endocrine diseases; and 4) malignant and premalignant lesions of the oral cavity. The Laboratory is organized around disease entities with a strong basic research program and a clinical arm. Because diseases do not recognize the boundaries of intellectual disciplines, the Laboratory is highly interdisciplinary.

The organizational structure of LOM is different than that of other laboratories within NIDR. Investigators with training and experience in different disciplines (e.g., virology, pathology, electron microscopy, cell biology, and clinical medicine and dentistry) are being brought together and asked to apply their expertise to particular diseases rather than concentrating on a particular discipline. Expertise that is applicable to several problems is being sought. For example, skills in virology, pathology and electron microscopy will be needed not only to study herpes simplex virus, but also aphthous ulcers, tumors of the oral cavity and salivary gland disease (Sjogren's disease).

Leadership will be provided by project co-ordinators. The role of the project co-ordinator will vary with the specific project, but in general it will be the responsibility of the co-ordinator to see that the project is moving, that materials and equipment are available, and that each member of the project knows what other members are doing. The project co-ordinator approach is being tried so as to give as much flexibility to the new program as possible. An individual may be a co-ordinator for one project and a member of the working staff in another. Hopefully, this will allow for maximal utilization of an individual's scientific talents and also provide an opportunity to develop and express one's ability as a leader and administrator. Projects and project co-ordinators will be phased in or out as scientific concepts evolve and as the emphasis of the overall program changes.

To increase the efficiency of the program and to prevent redundancy of effort two service units will be an integral part of the Laboratory. First, because most segments of the program require tissue culture facilities, a tissue culture production unit was created. By making routine cells available, a great amount of time is saved (i.e., one person prepares cells for all of the investigators in the Laboratory rather than each investigator preparing his own cells; moreover, this allows for a better quality control). The unit also serves to train new personnel in tissue culture techniques. The second service unit is concerned with histologic and microscopic techniques (e.g., immunofluorescence and electron microscopy). Since these techniques are required for almost every phase of the soft tissue program, a pathology service unit is being established. This unit will carry out three functions: 1) perform routine histology; 2) train new investigators and assist others in immunofluorescence and electron microscopy; and 3) conducts research

on specific aspects of the overall program.

To coordinate in a more efficient manner the efforts of the intramural and extramural program, members of LOM will serve in an advisory capacity to the extramural program (e.g., provide information on the latest and most promising scientific developments; point out areas where very little work is being done). In addition, frequent meetings are being held between the intramural and extramural program leaders. Use will also be made of workshops to help review the state-of-the-art in specific areas and formulate plans for future research. Several such workshops have already been held and others are in the planning stages. In addition, efforts are being made to initiate a collaborative program on oral tumors with the National Cancer Institute.

The staff of LOM was obtained by bringing together investigators from several areas within NIDR. The Virology Section of the Laboratory of Microbiology and Immunology provided the Virologists and the "Tissue Culture Service Unit". The Experimental Pathology Branch provided the expertise in histopathology and the nucleus of the "Pathology Service Unit". The Oral Medicine and Surgery Branch provided the clinicians. In addition, efforts are being made to recruit several new investigators with training in cell biology, "exocrinology", dermatology, and clinical medicine.

It was estimated that it would take about 2 years to make the program fully operational. Phase I, the reorganization phase, was completed in the 6-month period between March 1973 and September 1973. In that period, the organizational plans were formulated and NIDR personnel reassigned to the new program. Phase II, the developmental phase, is in progress and should be completed within the 18 months between September 1973 and March 1975. During this period, certain personnel will be retrained, new personnel will be hired and the staff will move into permanent quarters that have been specifically designed for the program needs of LOM.

Over the last 6 months LOM has laid plans for 4 new research projects which are either underway or about to be initiated. These projects have been made possible because of the reorganization and rely heavily on the inter-disciplinary nature of the new Laboratory. The projects include: 1) A double-blind clinical study on the treatment of aphthous ulcers with various drugs; 2) Efforts to isolate virus particles from aphthous ulcers, Behcet's Syndrome, and Sjögren's Syndrome; 3) Studies on the factors responsible for the persistence and reactivation of herpes simplex virus in the trigeminal nerve (an animal model is being used); and 4) Use of isoamylase enzyme patterns in the blood as a means of detecting and differentiating pancreatic disease from salivary gland disease. In collaboration with the extramural program, a state-of-the-art workshop on aphthous ulcers was held and plans have been made for a workshop on oral tumors.

Despite the turmoil which is naturally associated with any form of reorganization, these past 12 months have been highly productive in terms of the quality and quantity of scientific contributions (see Bibliography). Two of the most exciting and promising contributions came from the herpes project. Investigators in LOM have proposed a new hypothesis for how the

immune response of the host handles herpes simplex virus (HSV) infections. They believe that the immunological defense against HSV consists of two phases. The first is an immunologically specific antigen recognition phase and the second is a nonspecific effector phase. Their data suggest that it is the nonspecific effector phase which ultimately is responsible for halting the spread of herpes infection. They believe that the cellular immune response to HSV operates not by destroying virus-infected cells, but by producing interferon which inhibits viral replication in the surrounding uninfected cells. These studies not only offer new insight into the mechanism of defense against HSV, but may also provide leads for new therapeutic approaches in the treatment of this infection.

The second promising development comes from in vivo studies on the latency of HSV. Investigators in the Laboratory found that injection of the lips or vagina with HSV resulted in a latent infection in the local ganglion. Moreover, they found that by neurectomy they could reactivate the virus in the ganglion. This model offers the first real opportunity to study in a disciplined and quantitative manner the various factors that may be responsible for the reactivation of herpes in vivo. In addition, this model could prove to be a powerful tool for studying the effectiveness of various drugs and types of immunization on the prevention and treatment of HSV. Because of the flexible organizational structure of LOM much of the resources and facilities of the Laboratory will be devoted to this project over the next 12 months.

In other studies related to the salivary glands and pancreas, LOM investigators found that certain viruses (e.g., Coxsackie) can damage the acinar cells of the salivary gland and pancreas, but not the beta cells. At least one virus, a variant of encephalomyocarditis virus (EMC), can infect the beta cells of the pancreas. The resulting beta cell damage produces a diabetes-like syndrome in mice and the development of this syndrome is related to the genetic makeup of the mouse. These studies point to the possibility that some cases of human diabetes might also be due to viral infections and suggest that genetic factors may determine whether or not a particular individual will develop virus-induced diabetes. In related studies LOM investigators developed a quantitative technique for measuring serum isoamylase. Since there are two types of isoamylase in the serum, one coming from the pancreas and the other from the salivary glands, it is now possible to tell if a particular disease is damaging the salivary glands or pancreas by simply quantitating serum isoamylases. Attempts will be made over the next year to apply this technique to human diseases.

A detailed description of the individual projects follows.

Herpes Simplex Virus

Recurrent herpes simplex virus (HSV) infection is one of the most common viral afflictions of man. Neither the factors responsible for recurrence nor the mechanisms by which the host attempts to control this infection are clearly understood. Over the last year LOM has attempted to elucidate some of the problems associated with this viral infection by focusing on three main areas: 1) the immunological factors responsible for preventing the spread of infection both in vitro and in vivo; 2) the relationship of the

immune responses to the pathologic manifestations of the infection; and 3) factors responsible for the latency and reactivation of the virus.

For a number of years it has been suggested that cellular immunity plays an important role in the host defense against certain viral infections. It is now known that some viruses, such as HSV, can persist both in vitro and in vivo in the presence of high concentrations of neutralizing antibody. Data obtained in our laboratory over the last couple of years showed that anti-viral antibody plus complement could destroy monolayers of cells infected with HSV, but did not stop the spread of infection. Detailed studies on the relationship between time of appearance of viral antigens on the surface of infected cells and the susceptibility of these cells to immune lysis demonstrated that viral spread was always one step ahead of immune lysis, thus allowing the infection to persist. We then examined the possibility that factors which could disrupt the connection between contiguous cells or inhibit viral replication in adjacent cells might stop the viral spread. Our initial experiments showed that peritoneal exudate leukocytes, obtained from rabbits that had never been exposed to HSV, inhibited the spread of virus when added to monolayers of rabbit kidney cells infected with 15-20 pfu of HSV. A high concentration of leukocytes prevented the appearance of plaques and markedly reduced the virus titer when measured 72 hours later. Several lines of evidence showed that leukocytes in high concentrations were mildly toxic to the underlying cells; this prevented or inhibited the virus-induced cell fusion and thereby allowed antiviral antibody and complement to destroy the infected cell before cell-to-cell contact was re-established. There was no evidence for the presence of interferon in supernatant fluids of leukocyte cultures.

Over the last twelve months we have attempted to investigate the role of specifically sensitized lymphocytes in the defense against HSV. Rabbits were immunized with Freund's complete adjuvant; peritoneal exudate cells obtained from these animals were added to HSV-infected monolayers and purified protein derivative (PPD) was then added to stimulate the sensitized cells. Low concentrations of leukocytes, in the absence of PPD, did not inhibit viral replication. Only when the ratio of leukocytes to rabbit kidney cells exceeded 2.5 was viral replication inhibited. However, when both sensitized leukocytes and PPD were added, viral replication was inhibited an additional three to four logs. More importantly, PPD-stimulated leukocytes inhibited by over 90% when the ratio of leukocytes to kidney cells was as low as 0.1. Examination of the monolayers at these low concentrations of leukocytes failed to reveal any evidence of cytotoxicity as compared to higher concentrations of leukocytes. These results suggested the possibility that an immunologically induced mediator was being produced by the stimulated cells. When supernatant fluids from the stimulated cultures were added to uninfected monolayers for 12 hrs prior to infection with HSV, viral replication was markedly inhibited. Supernatant fluids from unstimulated cultures produced little if any inhibition. Since this mediator was non-dialyzable, did not sediment at 100,000 x g, was resistant to pH 2.0, was species specific and not HSV specific, we concluded that the viral inhibitor was immunologically-induced interferon. We then showed that leukocytes from animals specifically immunized with HSV can exert the same effects. In the

presence of HSV-sensitized leukocytes, UV-inactivated virus inhibited HSV replication in rabbit kidney cells by over 99%. In the absence of leukocytes, UV-inactivated virus did not inhibit HSV replication. As in the case of PPD, supernatant fluids from stimulated cultures contained interferon.

From these studies the following picture is beginning to emerge as to how the host defends itself against the spread of HSV. The immunological defense can be thought of as consisting of two phases. The first phase is an immunologically specific antigen recognition phase. Antiviral antibody, complement and immune lymphocytes react with virus or virus infected cells. This leads to the release of mediator derived from complement and lymphocytes which can attract inflammatory cells to the site of infection. In addition, other mediators such as lymphotoxin and interferon are released. The nonspecific phase of the defense consists of the action of these inflammatory cells and mediators on infected and adjacent uninfected cells, thereby breaking cell-to-cell contact and inhibiting viral replication. Because the virus spreads so rapidly to contiguous cells, the specific phase of the defense which destroys virus infected cells appears to have little affect on halting the infection. It is the nonspecific phase of the defense, that is, nonspecific cytotoxicity produced by inflammatory cells and lymphotoxin, and the inhibition of viral replication produced by immunologically-induced interferon, which appears to be responsible for finally stopping the cell-to-cell spread.

Because viruses, such as HSV, are rapidly lytic to cells, the role of immunopathology in acute viral infections has received relatively little attention; but it is becoming increasingly apparent that the immune response contributes in several ways to the pathologic manifestations of the infection. The second phase of our work was therefore concerned with determining whether host defense mechanisms contributed in any way to the pathological manifestations of HSV infection and whether deficiencies in the immune response are responsible for recurrent episodes of HSV infection.

Our results show that antibody and complement can destroy virus-infected cells in vitro before the virus itself destroys the cell. Moreover, antibody and complement exert this effect very rapidly, since immunological injury can be detected within 15 minutes after incubation of virus infected cells with antibody and complement. The interaction of antiviral antibody and complement with virus and virus-infected cells also activates the various components of the complement system. One of these components, C5A, is chemotactic for polymorphonuclear and mononuclear leukocytes and can attract inflammatory cells to the site of infection where they can exert their various effects, including nonspecific cell injury. Moreover, the interaction of immune lymphocytes with virus or virus-infected cells can lead to the release of a lymphocyte-derived chemotactic factor and lymphotoxin. Lymphotoxin can destroy both infected and uninfected cells.

Innumerable studies from many laboratories have failed to show any deficiency in antibody levels in patients with recurrent attacks of HSV. With the development of in vitro methods to evaluate cellular immunity we asked whether recurrent attacks might be related to deficiencies in cellular immunity.

We found that the peripheral blood leukocytes of seropositive but clinically negative patients could readily be stimulated by HSV antigens as measured by the incorporation of 3H-thymidine. Studies on patients with active recurrent lesions, showed that their lymphocytes could be stimulated to almost the same degree as seropositive but lesion-free subjects. The possibility that there was a deficiency in lymphokine production was next investigated. Lymphocytes from seropositive but lesion-free patients when exposed to HSV antigens *in vitro*, produced a factor that was chemotactic for mononuclear leukocytes. Similarly, lymphocytes from seropositive patients with active lesions also produced lymphotoxin. Thus, our studies failed to show any basic defect in the responsiveness ofthe lymphocytes that could account for recurrent attacks. These results suggest that the problem of recurrence does not lie in the immune response of the host, but rather in unknown factors responsible for the activation of HSV in the ganglia of the asymptomatic host.

The third area of investigation involved an attempt to study these factors by establishing an *in vivo* system of latent HSV infection in the ganglia of mice. Other investigators found that infection of mice by the footpad resulted in latent infection of dorsal root ganglia and that the virus could be recovered by explantation, but not by homogenization of the ganglia. In our study, both HSV-1 and HSV-2 were inoculated into mice by a variety of routes and attempts were made to recover the virus. HSV-1 was placed on the scarified cornea of mice and at different times thereafter the trigeminal ganglia were removed, homogenized and/or explanted. Virus could be recovered by either homogenization or explantation of ganglia for almost 2 weeks, but thereafter *only* by explantation. Similar results were obtained when virus was inoculated into the footpad and the dorsal root ganglia were assayed for virus. After two weeks, virus could not be recovered from any of 34 mice assayed by homogenization of the ganglia, while virus could be recovered from 40 out of 41 mice assayed by explantation of the ganglia. In addition, we found that inoculation of the lips with HSV-1 and the vagina with HSV-1 or HSV-2 resulted in a latent infection which could be detected by explantation but not by homogenization.

We then asked whether we could reactivate the virus. Because HSV was recovered after day 14, only when ganglia were explanted, virus detection by homogenization of the ganglia after this time was used as an index for measuring viral reactivation *in vivo*. Preliminary experiments revealed that cutting the sciatic nerve peripheral to the dorsal root ganglia, but close to the exit foramina of the spinal cord resulted in viral reactivation. Following neurectomy, HSV-1 could be recovered by homogenization of the dorsal root ganglia on days 2-5. In subsequent experiments ganglia were assayed for virus 3 days after surgery. Explantation of the ganglion from unoperative control animals showed that 100% were latently infected, while homogenization of the ganglion from either unoperated controls or animals sham operated at the hip or shoulders failed to yield virus. However, sciatic neurectomy resulted in viral reactivation in 20 out of 66 animals. Also, when sham operations were performed in the region of the exit foramina reactivation occurred in 4 out of 26 animals.

On the basis of these and other observations it appears that HSV resides in sensory ganglia. Our studies suggest that genital herpes resembles oral and ocular herpes in that local sensory ganglion may be the site of HSV latency, allowing periodic reactivation of the virus and recurrence of symptoms. The ganglia may thus serve as a reservoir for venereal transmission of herpes. The ability to reactivate HSV by neurectomy raises the question of whether more subtle stimuli acting upon sensory nerves might also reactivate the virus. The factors responsible for viral reactivation are of importance not only in understanding the pathogenesis of herpetic lesions, but also in regards to the association of HSV-2 with cervical cancer. Our studies demonstrating both the establishment of HSV latency in the lumbo-sacral ganglion following vaginal inoculation and the reactivation of the virus following nerve section raises the possibility that latent HSV, activated by the presence of a local tumor may travel down the sensory nerves and secondarily infect tumor cells. These possibilities are presently under investigation.

Aphthous Ulcers and Other Dermatologic Disorders

During the past year, LOM initiated a new research project entitled Aphthous Ulcers and Dermatologic Disorders. This new area of research will include diagnostic, virological and immunological investigations into the etiology of diseases such as Aphthous Ulcers, Behcet's disease, Sjogren disease and other related disorders.

During the past five years, the use of explant cultures has led to the successful isolation of viruses from a number of human diseases. A measles virus has been isolated from in vitro brain cultures from patients with subacute sclerosing panencephalitis. A papovavirus was isolated from patients with progressive multifocal leucoencephalopathy. Herpes virus type 2 was isolated from cervical tumor cells grown in tissue culture. The viruses of Kuru and Creutzfeldt-Jakob disease were shown to persist in cells grown in culture and a virus was isolated from brain cell culture derived from a patient with Crutzfeldt-Jakob disease. In light of these recent advances in viral isolation attempts, the use of explant cultures will be extensively employed in our studies.

Recurrent aphthous ulcers, Behcet's disease and Sjogren's syndrome are three disease states of unknown etiology with oral manifestations. Recurrent aphthous ulcers (RAU) are lesions found in man characterized by ulceration of mucosal tissues of the lips, cheeks, tongue, palate, gingiva, and pharynx. In addition, mucosal areas of the genital and anal surfaces may be involved.

Behcet's syndrome consists of recurrent oral and genital ulcers, iritis, retinitis, arthritis, skin lesions, GI lesions, and central nervous system involvement. Some people believe it is part of the aphthous spectrum, representing the most extreme form.

The etiology of Sjogren's syndrome is unknown. The disease is characterized by dryness of the eyes and mouth. Patients with Sjogren's syndrome, as well as systemic lupus erythematosus, dermatomyositis, and other related disorders have tubuloreticular structures (TRS) in their vascular endothelial cells

and leukocytes.

Despite the frequency and severity of these three disorders, very few attempts have been made to isolate viruses. Over the last 6 months we have obtained 1) ulcerative tissue biopsy; 2) lymphocytes; and 3) sera from patients with these diseases.

One part of each biopsy was fixed in formalin for histopathology and another part in gluteraldehyde for electron microscopy. Still another part of each biopsy was explanted and grown in vitro. Some cells have been in culture for 3 to 7 months and are in their 7th to 14th subculture. Although on occasions cytopathology has been observed, a viral agent has not yet been identified. Various specimens also have been inoculated into primary and continuous cell cultures (HEK, MA-184, WI-38, VERO, PRK) and blind-passaged two to three times. Cytopathic effects have not been observed in these cultures. In addition, the following techniques have been used to isolate and identify viruses: 1) fusion (Sandai virus) with continuous cell lines; 2) different growth conditions such as temperature, pH, arginine; 3) BUDR treatment; 4) hemadsorption; 5) hemagglutination with a variety of red blood cells; 6) herpes simplex virus interference studies; 7) inoculation of embryonating hens eggs and blind passage of the CAM; and 8) inoculation of newborn mice. Techniques used to demonstrate new antigens or antibody in the human specimens include: complement fixation, fluorescent microscopy, serum complement mediated cytotoxicity and lymphocyte stimulation.

Experiments by others have shown the presence of antibodies to fetal oral mucosa in the sera of patients with recurrent aphthous stomatitis. Since recurrent aphthous stomatitis is associated with genital and other lesions, as in Behcet's syndrome, the sera of patients with recurrent aphthous stomatitis has been examined for the presence of antibody to a genital mucosal extract of a newborn male using various immunologic techniques. Our previous work showed the presence of precipitating antibodies to the mucosal extract in the sera of four of eleven patients with recurrent aphthous stomatitis or Behcet's syndrome, but none of five patients with other stomatitides or none of 10 normal volunteers. The serum of a strong reactor has been analyzed and using various column chromatographic and immunologic techniques, the antibody activity has been shown to be localized to the IgM fraction. Attempts to characterize the genital antigen are in progress.

In conclusion, recent reports implicating adenovirus type one with the herpetiform type of aphthous ulcers, reports suggestive of a transmissible agent from Behcet's disease, and the presence of virus-like structures in Sjögren's disease all add credence to the possible etiology of these diseases. The results reported here describe our initial attempts to isolate viruses from patients with these disorders. Our laboratory will continue to investigate these disorders by following the procedures discussed and expanding our approaches to this problem.

Diseases of the Exocrine and Endocrine Glands

Our work in the endocrinology and exocrinology areas can be divided into two major areas: 1) viral infections of the salivary glands and pancreas, resulting in dysfunction of either or both of these organ systems; and 2) the development of isoenzyme techniques and their application to diseases of the salivary glands and exocrine pancreas.

Several lines of evidence suggested that viral infections might be involved in the development of human diabetes mellitus. First, a number of clinical case reports, as well as one epidemiologic study, have suggested a possible relationship between mumps virus and diabetes: however, this relationship has never been documented. Second, for over 20 years the Coxsackie B viruses have been known to infect the acinar pancreas in mice. More recently, epidemiologic studies have shown a possible increase in antibodies to Coxsackie B4 in newly-diagnosed diabetics. The third line of evidence suggesting a viral etiology of diabetes was the observation that the M variant of encephalomyocarditis (EMC) virus was capable of destroying pancreatic beta cells and inducing a diabetic syndrome.

Over the last couple of years we studied the EMC virus-induced diabetes system in mice. We found that infection of DBA/2 male mice with EMC virus resulted in a syndrome characterized by hyperglycemia, glycosuria, hypoinsulinemia, polydipsia and polyphagia. A marked degree of variability among male DBA/2 mice was noted in the development of this syndrome, and it was also shown that female DBA/2 mice, as well as males of other strains (CBA, C57BL/6, Balb/C, and A), did not become diabetic.

Work during the past twelve months has attempted to elucidate some of the variables within this virus-induced model of diabetes. Of prime importance was the demonstration that the development of diabetes could be correlated with the degree of pathologic destruction of the beta cells in the DBA/2 male. A linear correlation between the degree of hyperglycemia and the extent of pathologic damage was clearly demonstrated, both immediately after the acute infection and for periods up to one year.

In addition, by using direct immunofluorescence, the presence of large amounts of viral antigen in necrotic beta cells could be demonstrated, further strengthening the evidence linking the viral infection with the diabetic syndrome. When this technique was applied to female DBA/2 mice and to other strains it became apparent that in mice not developing overt diabetes, virus was not replicating significantly in the beta cells. The possible reasons for this difference in viral replication are presently under active investigation. Differences in cell surface receptors, differences in the immune response (either antibody or interferon), or differences in the hormonal environment are all possibilities under consideration.

Since the EMC virus seldom, if ever, produces overt human disease, it was felt necessary to investigate candidate human viruses as possible diabetogenic agents. Over the past year we have concluded extensive studies with the Coxsackie B group of viruses. All of these agents clearly possess the ability

to produce an acinar pancreatitis. This has been documented by: 1) routine histopathology; 2) direct immunofluorescence; 3) elevation of serum amylase levels during acute pancreatic necrosis (to levels as much as ten times normal); and 4) depression of pancreatic amylase content to levels less than five percent of normal following infection. Numerous efforts to elicit evidence of endocrine dysfunction (as manifested by hyperglycemia or by abnormal glucose tolerance) were unsuccessful under a wide range of experimental conditions.

Two other viruses, known to infect both the salivary gland and pancreas, were investigated during the past year in similar fashion. Murine cytomegalovirus was found to produce parotitis and exocrine pancreatitis, but no evidence of beta cell dysfunction was found. Studies with mumps virus, of particular interest because of the wide range of organs infected in man, were initiated, but have not yet resulted in the generation of a good animal model of disseminated infection.

The isoenzymes of amylase in human serum and in rodents have been extensively studied in the past. By electrophoretic techniques, especially with polyacrylamide gels, the separation of amylase into its salivary and pancreatic components can be effectuated. Past work in this laboratory has centered on the genetic aspects of the isoamylases. During the past year, two important new aspects of the isoamylase system were explored: 1) isoamylase separation was applied to humans with exocrine pancreatic insufficiency; 2) techniques were developed to quantitate isoamylases following electrophoresis.

Isoamylase zymogram patterns of serum, urine and duodenal fluid from cystic fibrosis patients with and without pancreatic insufficiency and normal subjects were studied. Our studies showed that in all patients with pancreatic insufficiency the diagnosis of deficient pancreatic function could be made by simply evaluating serum isoamylase zymograms. Therefore, duodenal intubation might have been avoided. Patients with normal pancreatic function had normal zymograms while all the cystic fibrosis patients had a low serum pancreatic isoamylase.

The limitations imposed on serum isoamylase analysis by the qualitative interpretation of zymograms were circumvented by the development of a technique to quantitate each fraction. The polyacrylamide gels were cut, the amylase eluted, and then each fraction analyzed for amylase content using the commercially-available blue starch substrate method. This technique was applied to mice previously infected with Coxsackie B viruses. During the acute infection, when serum amylase was elevated, isoamylase analysis showed that the hyperamylasemia was exclusively due to the pancreatic damage, even though the Coxsackieviruses often caused an associated parotitis. Of even more interest, however, were the findings after the subsidence of the acute pancreatitis. Although the serum amylase returned to normal levels, chronic pancreatic insufficiency could be diagnosed at this time by the decrease of pancreatic isoamylase in the serum. The serum amylase had remained normal because of the normal predominance of salivary isoamylase in the serum of the mouse. Thus, quantitation of isoamylases provided far more information

than could be derived either from the total serum amylase level or from the quantitative isoamylase patterns. Further studies are in progress applying isoamylase quantitation to human diseases.

Tumors of the Oral Cavity

Attempts were made to find markers for neoplastic cells by use of histochemical techniques. Mice were infected with polyoma virus and parotid tumors were stained for various enzymes. High activity of several enzymes including alkaline phosphatase, amino peptidase, and glutamyl transpeptidase were observed. It is hoped that one or more of these enzymes may ultimately prove useful for the early detection of transformed cells.

In the area of oral cancer and oral premalignant lesions two contracts remain in force. One is concerned with the epidemiology of oral cancer and oral premalignant lesions in rural India. The second is concerned with betel quid chemical carcinogenesis in baboons. Marked epithelial atypia was observed in the baboon cheek pouch mucosa after exposure to betel leaf, areca nut, lime and tobacco for 48 months. These observations coincide with the clinical findings in the rural Indian patients. The betel quid carcinogenesis study in baboons will be terminated in June 1974, while the rural India project will be continued for an additional three years.

Very little is known about the etiology of salivary gland tumors or the physiology of the salivary gland during malignancy. Consequently, a Salivary Gland Tumor Program has been formulated for LOM and areas of responsibility have been designated. A protocol for the collection, handling and preservation of specimens has been prepared and distributed to interested individuals. In brief, the research program will take three directions:

1) Cultivation of Normal and Neoplastic Salivary Glands in Vitro: Because of the difficulty in obtaining large quantities of salivary gland tissue from patients, studies in this area have been greatly handicapped. The establishment of continuous cell lines would by-pass this problem and could be extremely useful in studying products released from normal and malignant glands. Large amounts of these products could be collected, purified, and analyzed. If tumors of different cell types could be established (serous, mucous, ductal) a wide variety of products could be analyzed. By this means it might be possible to get a better understanding of the constituents of normal saliva.

2) Identification of Tumor Specific Products: Serum, saliva, and tumor homogenates will be analyzed for unique products of the tumor (e.g., tumor specific antigens). By this approach it might be possible to identify antigens such as alpha-fetoprotein and carcinoembryonic antigens which have been so useful in the diagnosis of hepatocellular carcinoma and colonic tumors, respectively. Attempts to find antibody in the serum and saliva which react with tumor-specific antigens might also prove to be a useful diagnostic procedure. Analysis of serum or saliva for isoamylase patterns by the quantitative techniques presently being developed by LOM also might prove to be a useful screening technique for the diagnosis of salivary gland tumors.

3) Salivary Glands as a Reservoir of Viruses: It is well known that viruses which grow in certain of the exocrine organs of the body (e.g., pancreas) will also grow in the salivary glands. Because the salivary glands are so easily accessible as compared to the pancreas, and because of the even greater ease in obtaining saliva, it might be possible to isolate viruses from this organ which in fact are producing disease in other exocrine glands (e.g., pancreas, gonads, or mammary glands). Accordingly, we propose to search for viruses in the salivary glands and saliva of patients with tumors of the pancreas and mammary glands. We also plan to carefully search for viruses or viral products in the saliva of patients with salivary gland tumors. In addition, efforts will be made to identify oncogenic viruses by looking for reverse transcriptase activity in the saliva and salivary glands. Finally, because it has recently been shown that cytomegalovirus (a member of the herpes group) can transform cells in vitro, and because this virus has been frequently isolated from the salivary gland of man, efforts will be made to identify the viral genome or products of the viral genome in tumors of the salivary gland.

The initiation and successful operation of this program depends on the availability of clinical material and properly trained personnel. It is hoped that at least a segment of this program will be initiated during the course of the coming year.

Clinical Studies

Recurrent aphthous stomatitis, despite its high incidence, frequency and severity, has not been objectively studied with regards to therapeutic regimes. Past reports of treatment programs were either anecdotal or insufficiently controlled. We felt that a careful, objective and double blind protocol involving the several most commonly used (and therefore potentially misused) drugs for the treatment of recurrent aphthous stomatitis was needed. Over the past year we developed a double blind protocol to determine the efficacy of tetracycline and prednisone versus placebo on the course of recurrent aphthous stomatitis in 36 patients. Appropriate statistical methods will be employed to assure random selection, medical safety, adequate evaluation, and reliable data gathering and interpretation. This protocol has been passed by the Clinical Research Committee of NIDR, and the Clinical Research Committee and the Medical Board of the Clinical Center, NIH. Over 100 patients have been screened so far, but to this date only 12 are acceptable for the study.

A broad program of investigation on the natural history and etiology of recurrent aphthous ulcerations also is in progress. Clinical information pertaining to the diagnosis, pathogenesis and therapy of recurrent aphthous ulcerations and Behcet's syndrome has been gathered. A protocol has been developed to obtain clinical materials (e.g., biopsies, vesicular fluid, and serum) from patients with recurrent aphthous ulcerations, Behcet's syndrome, and Sjogren's syndrome. This material will be worked up for infectious agents and immunological aberations.

Studies of Sjögren's syndrome have been concerned with (1) description of the natural history of the disease; (2) immunofluorescent and radioautographic techniques for detecting antisalivary duct antibody; (3) clarification of the role of lymphocyte which locally infiltrate the salivary glands and synthesize immunoglobulins (including rheumatoid factor); and (4) improved methods of detection and diagnosis.

The use of pilocarpine in the treatment of xerostomia in Sjögren's syndrome is planned. There is some evidence that pilocarpine may have a beneficial effect on the xerostomia in Sjögren's syndrome. The constant parasympathomimetic stimulation of the gland is thought possible to wash out inspissated debris and may prevent sludging and obstruction which contributes to pressure atrophy. With this in mind a protocol has been approved by the NIH Medical Board to study 6 patients and compare results with 6 normal volunteers (Parotid gland function will be monitored by sialometry, scintography and chamical analysis of the secretion).

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Summary Report of the Neurobiology
and Anesthesiology Branch
National Institute of Dental Research
Summary Statement

The Neurobiology and Anesthesiology Branch was established this year as part of the Institute's research initiative in the area of pain and pain control. Fundamental research on peripheral and central nervous system mechanims of oral-facial pain sensation is conducted by the Neural Mechanisms Section which was established in 1968 as a separate Section directly under the Office of the Director of Intramural Research. The Anesthesiology Section has been reestablished as part of the newly-formed Branch and in the future will broaden its research scope to include the development of objective and subjective measures of pain as well as the evaluation of pharmacological, psychological and sensory methods of pain control.

In the past year, the Neural Mechanisms Section has continued to employ a multidisciplinary approach in the study of pain mechanisms. Physiological studies have analyzed the peripheral nerve populations that respond to noxious or painful thermal stimuli applied to the monkey's face. These peripheral fibers terminate centrally in the trigeminal brain stem nuclear complex which has been intensively studied with neuroanatomical techniques by investigators in the Section. The substantia gelatinosal layer of trigeminal nucleus caudalis in the brain stem is morphologically distinct from other layers and may play a major role in the transmission of nerve impulses involved in pain sensation and reaction. Behavioral experiments in the Section have focused on the development of an animal model for the study of pain. Rhesus monkeys have been trained to escape noxious thermal stimuli in a reaction time paradigm. One of our major goals is to correlate central neuronal activity with behavioral performance in monkeys trained in this task.

The Anesthesiology Section at the moment is inactive and without personnel. Our plans for the next year are to recruit personnel interested in the study of clinical and experimental pain measurement and methods of pain control in the dental setting. The development of an active clinical research program is vital to the total program since it will provide the opportunity to relate our laboratory studies directly to clinical pain problems.

Report of the Clinical Investigations and
Research Services Branch
National Institute of Dental Research
Summary Statement

The Clinical Investigations and Research Services Branch was created August 7, 1973, as the result of a reorganization designed to facilitate more effective collaboration between the basic science laboratories and the existing clinical activities within NIDR. By administratively linking sections of the Laboratory of Microbiology and Immunology (LMI), and the newly established Laboratory of Oral Medicine (LOM) with two new clinical branches, it was anticipated that a more direct coupling between theory and application would result. The new clinical branches emerging from the reorganization are the Neurophysiology and Anesthesiology Branch (NAB) and the Clinical Investigations and Research Services Branch (CIR). The latter branch encompasses all of the activities of the former Dental Services Branch, i.e. the entire operation of the dental clinic including all existing research and clinical service responsibilities, as well as a section carried over from the former Oral Medicine and Surgery Branch (Oral and Pharyngeal Development Section) and an entirely new enterprise, the Clinical Investigations Section. The latter is devoted exclusively to basic methodological and applied clinical research. Under the direction of the Clinical Director, CIR also coordinates all collaborative research activities involving human subjects, particularly those activities interfacing in the dental clinic.

The basic strategy underlying this administrative structure was to foster a more efficient means for capitalizing on the diversity of patients and resources available at the Clinical Center. Since many patients are referred for dental consultation and treatment from other Institutes, it was felt that with suitable planning, referred patients might simultaneously participate in a variety of clinically based dental research projects.

Initial efforts to implement such an approach are based on a cross-sectional study of the role played by specific oral microflora in dental patients presenting a variety of local and systemic manifestations of dental disease. All patients routinely seen in the clinic which conform with protocol requirements, are thus considered potential sources of clinically meaningful data and are urged to cooperate to this end. Other efforts which uniquely complement existing resources include studies designed to test various treatment modalities, and clinical evaluation of new diagnostic tools. These tools are currently being developed within the Branch by a small group which is primarily concerned with the theoretical delineation of factors limiting the performance of clinical systems. This activity also complements long-range plans for collaborative research with the Neurophysiology and Anesthesiology Branch involving human subjects.

In order to accommodate the planned increase in clinical research activity, considerable attention has been directed toward the introduction of operational changes, such as automated record keeping and augmented technical activity. The diversity of this approach is demonstrated further

by the introduction of a clinical unit which explicitly coordinates preventive maintance on the part of the patient with therapeutic as well as surgical treatment of various dental disorders.

Another aspect of the Branch activity involves continued efforts to more adequately describe structure and function of the oral pharyngeal area. This work has been the center of interest of the Oral and Pharyngeal Development Section for several years and has found a new home within CIR as a result of the reorganization cited earlier.

The altered perspective engendered by the systems orientation of the Branch, complements the scholarly contributions of this Section by affording more convenient access to newly developed technological resources.

As the clinical sections of LOM and LMI evolve, it is anticipated that additional collaborative research will ensue thus further capitalizing on the multidisciplinary resources available within CIR.

Report of the Clinical Dental Services Section
Clinical Investigations and Research Services Branch
National Institute of Dental Research
Summary Statement

The Clinical Dental Services Section provides the new interface for patient contact within NIDR. It has primary responsibility for providing both clinical and collaborative support to all NIH intramural programs involving dental treatment and associated clinical research. Although it retains all of the functions of the former Dental Services Branch, which it replaces, it is challenged by being forced to operate with an even smaller staff. In spite of this and the fact that slightly over 50% of the patients seen in the dental clinic continue to be referred for dental consultation and treatment from other Institutes, this Section is bolstering its commitment to dental research.

This is being accomplished by altering the spectrum of research activity to incorporate more cross-sectional studies, capitalizing on the availability of patients referred for obligatory dental treatment. Although this reduces to some extent the option for longer range longitudinal investigations, past experience has shown that such studies are often difficult to manage and relatively expensive to maintain.

Initial efforts have centered around routine screening of dental patients for specific serological types of potentially pathogenic microflora. This and other related studies are discussed in the Summary Report of the Clinical Investigations Section.

Another approach which capitalizes on the relatively short-term availability of patients, involves the determination of immunological characteristics of human periodontal disease. This is accomplished by comparing such factors as lymphocyte transformation reactivity, soft tissue T and B type lymphocyte differentiation processes, and specific antibody response mechanisms. The comparisons are being made both pre- and post treatment on subjects with moderate to severe periodontal defects. This work is being done in collaboration with Drs. Oppenheim and Chused of the Laboratory of Microbiology and Immunology, and Dr. Baker and Sue Chan of Litton Bionetics, Bethesda, Md.

Logistical modifications are also being implemented in anticipation of additional interaction with the Laboratory of Microbiology and Immunology (LMI), as well as planned collaboration with the Neurophysiology and Anesthesiology Branch (NAB), and the Laboratory of Oral Medicine (LOM). These modifications include a broadening of the scope of responsibility of all clinic personnel to include specific types of research activity, automation of record keeping procedures, and the reallocation of space to more conveniently accommodate anticipated research.

During the interim, the Section is in the process of completing two existing studies, one dealing with the radiographic visibility of induced skull fractures which was done in collaboration with Dr. John

Doppman of the Clinical Center Diagnostic Radiology Department, and the other being an electron microprobe and X-ray diffraction study of the gamma$_2$ (mercury-tin) phase present on dental amalgam surfaces. The latter study relates to the mechanism underlying corrosion of amalgam restorations and was done in collaboration with Mr. Richard Waterstrat, ADA Research Associate, National Bureau of Standards, and Drs. Eanes and Greenfield of the Laboratory of Biological Structure.

Other research of a more transitory nature has been also initiated as a means for supplementing the long-range plans for coordinated activity with the basic science laboratories cited earlier. Such research not only fills the gap between planning and implementation of more comprehensive studies, it also provides a unique opportunity for clinical personnel to participate in a broad spectrum of research activity and, hence, acquire valuable experience which will facilitate future collaborative efforts. The following projects are thus being implemented with these goals in mind:

Rhesus Monkey Intraosseous Implant Study

The effect of functional occlusal loading on supporting tissues is being accessed in a controlled fashion through serial quantitative radiographic analysis of apparent calcification of subjacent bone, and terminal histological examination of both splinted and free-standing acrylic implants.

Lavage Volumes in Third Molar Surgery

Clinical Evaluations are being performed on the effects of various lavage modalities on post-surgical healing of third molar extraction sites.

Transient Bacteremias Related to Oral Surgical Procedures

Four different projects are combined in this multifaceted study. They involve respectively:

a) Effects of topical pretreatment of surgical areas with various antiseptics on the induction of bacteremias.

b) Application of the nitroblue tetrazolium dye test in evaluating surgically induced bacteremias.

c) Comparative evaluation of blood culture media for the recovery of anerobic organisms, and

d) Evaluation of endo-toxemia in transient bacteremias.

These combined projects are being done in collaboration with Drs. Brenner and Elin of the Clinical Pathology Branch of the Clinical Center and Dr. Chusid of the Laboratory of Clinical Investigations, NIAID.

As the clinical program continues to develop it is self-evident that staffing at the existing level will prove inadequate. Efforts are therefore underway to explore all possibilities for supplementing available personnel to provide even the minimal human resources required for responsible performance.

Marginal staffing, however, has spotlighted the need for more efficient management of dental disorders. This necessity has resulted in a more explicit patient education program which combines individualized preventive home care instruction and demonstration with a specific self treatment regimen whenever appropriate. This new program is being coordinated and personally supervised by Dr. Paul Keyes of the Clinical Investigations Section. Hopefully, the link between research and application exemplified by such affiliation will assure even more productivity in the future.

Report of the Clinical Investigations Section
Clinical Investigations and Research Services Branch
National Institute of Dental Research
Summary Statement

The Clinical Investigations Section is a multidisciplinary enterprise which combines the professional talents of basic scientists with research oriented clinicians for the purpose of initiating and facilitating clinical research. The main thrust of this group, is to develop and implement diagnostic standards applicable to clinical investigations of all types. Of particular interest, is the problem of detecting deviations from normal, i.e. physical, physiological, biochemical, or microbiological deviations.

For many of the destructive diseases that affect the tissues of the mouth, the principal evidence of abnormality is the gross loss of tissue. e.g. ulceration, cavitation of the teeth (dental caries), and periodontal pocketing. Since microflora play an essential role in the processes leading to odontolysis and the loss of periodontal tissue, a high priority has been placed on the investigation of microbiological methods which might permit one to conveniently assess potentially pathologic processes. If one could follow and periodically assess the germ life attached to teeth, including the associated biochemical activity, it would be possible to do four things: 1) predict potentially hazardous conditions before actual destruction occurs; 2) follow the effect of therapeutic measures prescribed for the control of active disease; 3) know when intensive therapeutic measures can be terminated, and 4) anticipate the need for further therapy in the case of remission.

There is evidence that at least three types of microbial populations may be significant: 1) Streptococcus mutans and S. mutans-like cocci; several strains of actinomyces; and the motile flora.

Work is in progress to determine the prevalence of S. mutans in all suitable patients examined in the dental clinic. As work progresses, cases will be studied to determine if there be any correlation between the various serological types of S. mutans and the past and future status of cavitation. Associated technical questions include establishing bases for developing efficient serological screening procedures as well as appropriate methodology for sampling and plaque dispersion. Indices being considered include: 1) the fraction of total culturable streptococci comprised by S. mutans; 2) quantitative accessment of relative number of inflammatory cells associated with plaque samples; and 3) specific assay of promising enzyme systems. Planned collaboration with Drs. London, Hageage, and Wittenberger, link this work with NIDR's Laboratory of Microbiology and Immuniology.

Another project has been initiated as a result of phase-contrast microscope examinations of dental plaque. Observations in patients with rapidly advancing periodontal detachment without calculus and gross gingivitis reveal high numbers of largely unidentified motile bacteria.

Although the pathogenic potential of these microorganisms is as yet unknown, they appear to be particularly prevalent in such periodontally involved patients. As the numbers of organisms involved are so enormous and their activity so great, it seems unlikely that they lack clinical significance. Hence, efforts are being made to see how they respond to conventional periodontal therapy. Preliminary observations indicate that neither conservative scaling by a professional nor routine oral hygiene measures by patient are effective in controlling these populations. As a consequence, an investigation is under way to study the effect of supplementary antibiotic therapy, e.g. tetracycline HCl. The effect of this drug on the actinomycotic flora, and on S. mutans is likewise being determined.

A few patients and a group of Patus monkeys with periodontal lesions have been sampled to determine the prevalence of certain strains of actinomyces, namely A. viscosus, A. israelii, and A. naeslundii. Although lack of manpower has delayed full evaluation of the material at hand, preliminary data are consistent with findings in lower animals, i.e. some actinomyces are highly invasive and destructive in monoinfected rats. Accordingly, it continues to be of interest to determine if any of these microorganisms are prevalent in cases of human and/or primate periodontal disease.

There appears to be enough evidence at present to suggest that judicious chemotherapy should play a larger role in the control of infections conducive to dental caries and periodontal disease. This approach will be explored more rigorously as methods for assessing the bacteria in plaque become available.

Another important research consideration of the Section is the development of improved diagnostic tools, particularly with respect to identification of factors limiting diagnostic performance. Accordingly, an attempt has been made to assess various diagnostic tasks from the point of view of information theory so as to determine if lack of channel capacity is limiting performance under clinical conditions. In at least one instance, there is evidence to suggest that diagnosis is not capacity limited. Recent experiments have shown that the detection of incipient interproximal caries from bitewing radiographs is not significantly influenced by the introduction of statistical noise. This finding suggests that it is theoretically possible to improve diagnostic performance while at the same time reducing patient exposure to ionizing radiation. A new radiographic system has been developed and is currently being tested which capitalizes on this finding by reducing required radiation more than an order of magnitude, while at the same time yielding Polaroid prints which are available for interpretation seconds after exposure.

Related research is also underway which involves classification of clinical radiographs containing evidence of known pathology in terms of the spectrum of spatial frequencies required for reliable performance of appropriate diagnostic tasks. Once specified in this way, it becomes theoretically possible to analyze the effect of various preprocessing schemes on the apparent channel capacity required for diagnostic perform-

ance. As a result, optimization of related diagnostic procedures can be approached more systematically.

Although current restrictions in personnel and facilities preclude a more comprehensive approach to methodological development of clinical research, enough progress has been made already to assure sound theoretical bases for meaningful investigations in this area.

Report of the Oral and Pharyngeal Development Section
Clinical Investigations and Research Services Branch
National Institute of Dental Research
Summary Statement

The activities of this Section continue to be concerned with the development of structure and the development of function in the oral and pharyngeal area.

This is the fifth year of gross anatomical studies of the pharynx and cranium of the human fetus at term. The anatomical and radiological illustrations for the Atlas of Anatomical Sections and Tomograms of the Newborn are completed, labelled and legended. The descriptive chapters are in final revision. The book is to be reviewed in May and June.

Text drafting and illustration of a general anatomy of the face, pharynx and larynx of the newborn continue. The portion concerned with the skeleton is completed in illustration. Ms. Beverly Etter, medical illustrator, has been replaced by Ms. Diane Murayama, and we are now dissecting and illustrating the epipharynx, muscular palate and eustachian apparatus in a series of 18 illustrations. Comparable studies of the larynx and lower pharynx region will complete the illustrations for this volume.

The histological studies of the newborn infant lip have been completed by Dr. Thach and are in Press in the Fourth Symposium on Oral Sensation and Perception (estimated publication: June, 1974), and also have been submitted to the Journal of Anatomy.

Illustrations and most of the text of the book, Development of the Rat Skull (by Melvyn Baer, James Bosma and James Ackerman) are completed. A set of 120 projection slides have been assembled in page-size plastic holders for each of the prospective 1200 issues of this book. Submission of this book for estimation of publication costs is scheduled for this summer. Grant application for sponsorship of this publication will be submitted to the National Library of Medicine Extramural Program prior to October 1, 1974.

We continue to engage in a small number of clinical anatomical studies, particularly of arrhinia and of arrhinencephaly.

In the current year, our physiological studies have continued to concentrate upon oral reflexes of the infant. The development of the specific transverse tongue response has now been worked out in the premature infant. These findings have been reported at pediatric and psychology meetings. Two chapters in the Fourth Symposium on Oral Sensation and Perception (in press) are now under consideration by journals.

In a notable extension of the latter studies, the transverse tongue response has been found useful in the evaluation of responses to a tastant applied to the tongue. This demonstration of taste discrimination in newborn infants appears to provide the basis for new concepts of the possible genesis of taste preferences, particularly that for sweet. By relating his own findings to studies of the relation of taste to ingestion in lower mammals, Dr. Weiffenbach has found correlative indications of a strategic role of early postnatal taste and other feeding experience in the determination of later dietary patterns. This is of considerable significance apropos of dietary distortions of various kinds. Dr. Weiffenbach is now engaged in assembling a conference of investigators in disciplines ranging from developmental neurophysiology and psychology, to nutrition and nutrition-related disorders to examine the genesis of taste preferences in man.

Our previous and current work and our assemblage of studies by others on the topic of sensorimotor performances of the mouth and pharynx of infants has continued in publications derived from the conferences. Publication of the Fourth Symposium on Oral Sensation and Perception: Development in Fetus and Infant is scheduled in June, from the Government Printing Office. A Fifth Symposium is in plan. The NIDR, in ccoperation with the National Institute of Child Health and Human Development, and the Fogarty International Center, is sponsoring a Symposium on Development of Upper Respiratory Form and Function, in April; this is intended for commercial publication. The work of our group on development of sensorimotor functions is scheduled for inclusion in a University of Michigan Symposium on Oral Development, in April.

Sponsorship of the clinically-pertinent cinema, "Examination of the Mouth and Pharynx of the Infant" has now been arranged by this Institute. Final filming and preparation of matching script and of drafting correlative brochure is scheduled for May and June.

Clinical applications of these studies of mouth, pharynx and larynx function are accumulating. Selected cinema and other demonstration material will be used in a University of North Carolina Symposium on Evaluation of the Neurologically Impaired Infant, in May. We continue consultations with Clinical Center patients of other Institutes, particularly apropos of disabilities of the pharyngeal area. J. Bosma is also working in collaboration with the Departments of Radiology and Neurology of the Johns Hopkins Medical Center in a study of pharyngeal disabilities of the mature human.

PART V

NATIONAL INSTITUTE OF DENTAL RESEARCH

ANNUAL REPORT

COLLABORATIVE RESEARCH PROJECTS

July 1, 1973 - June 30, 1974

Compiled by

Dental Research Data Officer

National Institute of Dental Research

National Institutes of Health

Bethesda, Maryland

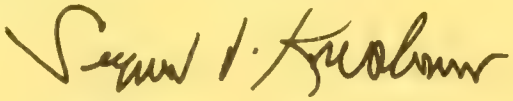
PREFACE

The NIDR Annual Report is intended to capture in printed form the essence of the Institute's total activities during the course of one fiscal year. The present format has evolved from our desire to make the Report more palatable to the reader, a better reference tool for its users, and less burdensome in preparation for its contributors.

A major change in compilation has been made in this issue to accommodate our several uses of the completed document. The Report for FY 1974 has been prepared in organizationally distinctive Parts to facilitate selective distribution to those who are concerned with or require as a working instrument less than the total publication. These are: Part I, Office of the Director, Research Projects and Indexes; Part II, National Caries Program; Part III, Extramural Programs; Part IV, Intramural Research; and Part V, Contracts.

For the third year, we have continued the practice of using a modified SSIE Notice of Research Project form (PHS 166) for the Individual Project Report. These are collected together as a section of Part I. This section, on blue paper, is accompanied by a number of indexes, for ease of retrieval and analysis, and a Classification Guide to Subjects and Categories.

We apologize in advance for any errors that may have escaped our attention and would appreciate your comments and suggestions so that we may continue to improve this document in the future.



Seymour J. Kreshover, D.D.S., M.D.
Director
NIDR

CONTENTS

PART I - OFFICE OF THE DIRECTOR

PART I - RESEARCH PROJECTS AND INDEXES

PART II - NATIONAL CARIES PROGRAM

PART III - EXTRAMURAL PROGRAMS

PART IV - INTRAMURAL RESEARCH

PART V - COLLABORATIVE RESEARCH PROJECTS PAGE

Preface iii

Contents v

Indexes

Research Projects Projects by Organization vii

Research Projects by Project Director ix

Research Projects by NIDR Project Officer xi

Research Projects by NIDR Specialist xiii

Research Projects by Number xv

Research Projects by Subject Area xvii

Interagency Agreements 1

Contracts 17

INDEX

COLLABORATIVE RESEARCH PROJECTS BY ORGANIZATION

ORGANIZATION	PAGE
AMERICAN DENTAL ASSOCIATION	121
AMERICAN DENTAL ASSOCIATION	113
AMERICAN DENTAL ASSOCIATION	105
AMERICAN DENTAL ASSOCIATION	67
BATTELLE MEMORIAL INSTITUTE	17
BATTELLE PACIFIC NORTHWEST LABORATORIES	57
CANCER RESEARCH CENTER	87
CENTER FOR DISEASE CONTROL, HSMHA	7
CENTER FOR DISEASE CONTROL, HSMHA	9
CENTRAL INSTITUTE FOR EXPERIMENTAL ANIMALS	95
CLEMSON UNIVERSITY	107
DEPARTMENT OF NAVY	3
DUKE UNIVERSITY	73
EASTMAN DENTAL CENTER	65
EASTMAN DENTAL CENTER	49
FORSYTH DENTAL CENTER	55
FORSYTH DENTAL CENTER	45
FORSYTH DENTAL CENTER	151
FORSYTH DENTAL CENTER	39
FORSYTH DENTAL CENTER	37
FORSYTH DENTAL CENTER	137
FORSYTH DENTAL CENTER	125
FRANKLIN INSTITUTE	19
GENERAL MILLS, INC	99
GULF SOUTH RESEARCH INSTITUTE	117
HARVARD UNIVERSITY	111
HARVARD UNIVERSITY	51
HAZELTON LABORATORIES INCORPORATED	129
HEALTH RESEARCH, INC	29
HOWARD UNIVERSITY	25
HUNTINGTON RESEARCH CENTER	83
INDIAN HEALTH SERVICE, HSMHA	1
INSTITUTE FOR TECHNOLOGIC INVESTIGATIONS	127
LITTON BIONETICS, INC	101
LITTON BIONETICS, INC	91
MEDICAL COLLEGE OF GEORGIA	35
MIDWEST RESEARCH INSTITUTE	53
NATIONAL BUREAU OF STANDARDS	11
NATIONAL BUREAU OF STANDARDS	15
NATIONAL BUREAU OF STANDARDS	5
NEW YORK MEDICAL COLLEGE	103
NEW YORK STATE UNIVERSITY	141
PENNSYLVANIA STATE UNIVERSITY	71

ORGANIZATION PAGE

RESEARCH FOUNDATION OF STATE UNIVERSITY OF NY..... 79
ROYAL COLLEGE OF SURGEONS OF ENGLAND..... 97
ROYAL DENTAL COLLEGE..... 61
SOUTHERN ILLINOIS UNIVERSITY..... 31
SOUTHERN RESEARCH INSTITUTE..... 153
SOUTHERN RESEARCH INSTITUTE..... 131
SOUTHWEST FOUNDATION RESEARCH & EDUCATION..... 157
SOUTHWEST FOUNDATION RESEARCH & EDUCATION..... 155
STATE OF FLORIDA - DIVISION OF HEALTH..... 119
THE KENDALL COMPANY..... 159
UNION CARBIDE CORPORATION..... 133
UNIVERSITY OF ALABAMA..... 47
UNIVERSITY OF ALABAMA..... 63
UNIVERSITY OF CALIFORNIA..... 75
UNIVERSITY OF CALIFORNIA..... 139
UNIVERSITY OF CALIFORNIA..... 115
UNIVERSITY OF CONNECTICUT..... 135
UNIVERSITY OF FLORIDA..... 109
UNIVERSITY OF FLORIDA..... 77
UNIVERSITY OF IOWA..... 143
UNIVERSITY OF IOWA..... 123
UNIVERSITY OF MIAMI..... 69
UNIVERSITY OF MIAMI..... 21
UNIVERSITY OF MICHIGAN..... 147
UNIVERSITY OF MICHIGAN..... 85
UNIVERSITY OF MINNESOTA..... 81
UNIVERSITY OF MINNESOTA..... 93
UNIVERSITY OF MINNESOTA..... 41
UNIVERSITY OF MINNESOTA..... 33
UNIVERSITY OF OREGON..... 149
UNIVERSITY OF PENNSYLVANIA..... 89
UNIVERSITY OF PUERTO RICO..... 27
UNIVERSITY OF TEXAS AT HOUSTON..... 43
UNIVERSITY OF UTAH..... 23
UNIVERSITY OF WASHINGTON..... 145
VETERANS ADMINISTRATION HOSPITAL..... 13
WORLD HEALTH ORGANIZATION..... 59

INDEX

RESEARCH PROJECTS BY PROJECT DIRECTOR

PROJECT DIRECTOR	PAGE
ANDERSON, RAY H.	99
BAGRAMIAM, ROBERT A.	85
BAHN, ARTHUR N.	31
BARMES, DAVID E.	59
BIBBY, BASIL G.	65
BOYD, DALE D.	129
BREED, L W.	53
BURNETT, GEORGE W.	35
BUTTS, JOHN.	1
CAGAN, ROBERT H.	89
CASSEL, JAMES M.	15
CHERRY, WILLIAM B.	7
COLE, MICHAEL F.	97
CONS, NAHAM C.	29
COWSAR, DONALD R.	153
DANIELS, CHARLES A.	73
DE PAOLA, PAUL F.	45
DE PAOLA, PAUL F.	39
DEPAOLA, PAUL F.	151
DREIZEN, SAMUEL.	43
ENGLISH, JAMES A.	79
ENWONWU, CYRIL.	145
FINN, SIDNEY.	47
FOLKE, LARS E A.	41
FRANKLIN, ALAN D.	5
GENCO, ROBERT J.	141
GLASS, ROBERT L.	55
GRAVES, RICHARD C.	147
GROBMAN, HULDA.	113
GUERRA, OSCAR N.	87
HARRIS, NORMAN O.	27
HEFFERREN, JOHN J.	121
HEFFERREN, JOHN J.	67
HILLMAN, ROBERT E.	17
KEENE, HARRIS J.	3
KINGSBURY, ELIZABETH.	101
KLAWITTER, JEROME J.	107
KOULOURIDES, T.	63
LILJEMARK, WILLIAM F.	93
LILJEMARK, WILLIAM F.	81
LOBENE, RALPH R.	125
LOSEE, FRED L.	49
LU, KUO H.	149

PROJECT DIRECTOR

	PAGE
MACKENZIE, IAN C	143
MACKLER, BRUCE F	91
MARSHALL, ROBERT P	57
MASHBERG, ARTHUR	13
MELLBERG, JAMES R	159
MONCADA, FELIX	127
MUNGER, BRYCE L	71
NAVIA, JUAN M	75
NISHIMURA, HIDEO	95
OLSON, GERALD A	77
PICKARD, LUCILLE G	9
PULLMAN, IRA	103
RAWLS, HENRY R	117
REED, O M	155
REED, O M	157
RINGELBERG, MEL	119
ROBESON, LLOYD M	133
SCHACHTELE, CHARLES	33
SCHIOTT, D RINDOM	61
SHAW, JAMES H	51
SHULMAN, LEONARD B	111
SILVERSTEIN, STEVEN	115
SONI, NADAR	25
STANLEY, HAROLD R	109
STEFFEK, ANTHONY J	105
TANQUARY, A CHARLES	131
TANZER, JASON M	135
TAUBMAN, MARTIN A	137
TAUBMAN, MARTIN A	37
THELEN, EDWARD	19
TORCHIA, DENNIS A	11
WEI, STEPHEN H	123
WILLIAMS, M L	23
WILSNACK, ROGER E	83
WYCOFF, SAMUEL J	139
ZINNER, DORAN D	21
ZINNER, DORAN D	69

NIDR ANNUAL REPORT - FY 74

INDEX

RESEARCH PROJECTS BY NIDR PROJECT OFFICER

NIDR PROJECT OFFICER	PAGE
BOSMA, JAMES F	71
BOWEN, WILLIAM H	139
BOWEN, WILLIAM H	129
CARLOS, JAMES P	61
CHASSEY, BRUCE	127
CHRISTIANSEN, R L	95
DRISCOLL, WILLIAM.S	85
DRISCOLL, WILLIAM.S	119
ENGLANDER, HAROLD.R	159
ENGLANDER, HAROLD.R	3
FOWLER, BRUCE O	5
FOWLER, BRUCE O	103
FRAZIER, PAUL D	145
FRAZIER, PAUL D	143
FREW, RALPH A	117
FREW, RALPH A	113
FREW, RALPH A	29
FREW, RALPH A	27
FREW, RALPH A	47
GIBSON, WILLIAM A	101
HAGEAGE, GEORGE J	83
HAGEAGE, GEORGE J	9
HAMNER, JAMES E	155
HAMNER, JAMES E	157
HAYES, RICHARD L	13
HEIFETZ, STANLEY.B	151
HEIFETZ, STANLEY.B	149
IKARI, NORMAN S	137
IKARI, NORMAN S	31
IKARI, NORMAN S	41
IKARI, NORMAN S	37
IKARI, NORMAN S	93
IKARI, NORMAN S	87
IKARI, NORMAN S	81
IKARI, NORMAN S	77
IKARI, NORMAN S	63
JOHNSTON, MALCOLM.C	105
JOLY, OLGA	79
JOLY, OLGA	147
JOLY, OLGA	49
JOLY, OLGA	45
JOLY, OLGA	55
JOLY, OLGA	39

NIDR PROJECT OFFICER PAGE

KAKEHASHI, SAMUEL 17
KAKEHASHI, SAMUEL 23
KAKEHASHI, SAMUEL 19
KAKEHASHI, SAMUEL 133
KAKEHASHI, SAMUEL 131
KAKEHASHI, SAMUEL 111
KAKEHASHI, SAMUEL 109
KAKEHASHI, SAMUEL 107
KAKEHASHI, SAMUEL 57
KAKEHASHI, SAMUEL 53
KAKEHASHI, SAMUEL 67
KAKEHASHI, SAMUEL 15
KORTS, DAVID C 121
KORTS, DAVID C 123
LARSON, RACHEL H 97
MARTIN, GEORGE R 11
MERGENHAGEN, STEPHAN 91
MEYERS, RHEA 115
MIRTH, DALE B 153
NOTKINS, ABNER L 73
RIZZO, ANTHONY A 135
RIZZO, ANTHONY A 141
ROGERS, WILLIAM E 65
ROGERS, WILLIAM E 51
ROGERS, WILLIAM E 75
ROGERS, WILLIAM E 99
ROUSSOS, GERASSIMOS 89
ROUSSOS, GERASSIMOS 33
SENNING, RICKLEY.S 21
SENNING, RICKLEY.S 59
SHERN, ROALD J 69
SHERN, ROALD J 35
SHERN, ROALD J 125
STILES, HORACE M 25
STILES, HORACE M 43
THOMSON, L ARIEL 7
THOMSON, L ARIEL 1

NIDR ANNUAL REPORT - FY 74

INDEX

RESEARCH PROJECTS BY NIDR SPECIALIST

NIDR SPECIALIST	PROJECT NUMBER	PAGE
BLEVINS, MARION	N01 DE12332-03	035
	N01 DE12381-03	049
	N01 DE12382-04	051
	N01 DE12383-06	053
	N01 DE22039-03	065
	N01 DE22045-01	067
	N01 DE22401-01	071
	N01 DE22402-02	073
	N01 DE22410-02	085
	N01 DE22413-02	089
	N01 DE32408-01	097
	N01 DE32416-00	099
	N01 DE32418-01	103
	N01 DE32419-01	105
	N01 DE32428-01	121
	N01 DE32429-01	123
	N01 DE42437-01	135
	N01 DE42440-01	141
	N01 DE42441-01	143
	N01 DE42442-01	145
	N01 DE42446-01	153
	Y01 DE20005	001
	Y01 DE30011	007
	Y01 DE30012	009
	Y01 DE40014	013
KEEFER, DAVID	N01 DE02238-06	019
	N01 DE12013-05	021
	N01 DE12022-05	023
	N01 DE12041-03	025
	N01 DE12062-06	027
	N01 DE12093-05	029
	N01 DE12330-04	031
	N01 DE12377-06	043
	N01 DE22003-05	059
	N01 DE22400-02	069
	N01 DE22406-01	079
	N01 DE22409-02	083
	N01 DE32420-01	107
	N01 DE32421-01	109
	N01 DE32422-01	111
	N01 DE32423-03	113

NIDR SPECIALIST	PROJECT NUMBER	PAGE
KEEFER, DAVID	N01 DE32424-01	115
	N01 DE32425-01	117
	N01 DE42434-01	129
	N01 DE42435-01	131
	N01 DE42436-01	133
	N01 DE42443-01	147
	N01 DE42444-01	149
	N01 DE42445-01	151
	N01 DE71475-10	155
	N01 DE71476-10	157
	N01 DE81262-07	159
	Y01 DE20006	003
MULLEN, EDITH	N01 DE02237-04	017
	N01 DE12331-04	033
	N01 DE12333-03	037
	N01 DE12375-07	039
	N01 DE12376-04	041
	N01 DE12379-06	045
	N01 DE12380-04	047
	N01 DE12384-03	055
	N01 DE12386-04	057
	N01 DE22005-04	061
	N01 DE22030-05	063
	N01 DE22403-02	075
	N01 DE22404-02	077
	N01 DE22407-02	081
	N01 DE22412-02	087
	N01 DE22414-03	091
	N01 DE22415-01	093
	N01 DE32405-01	095
	N01 DE32417-01	101
	N01 DE32427-01	119
	N01 DE32430-01	125
	N01 DE42431-01	127
	N01 DE42438-01	137
	N01 DE42439-01	139
	Y01 DE30010	005
	Y01 DE30013	011
	Y01 DE40015	015

NIDR ANNUAL REPORT - FY 74

INDEX

COLLABORATIVE RESEARCH PROJECTS BY NUMBER

IDENTIFICATION NUMBER	PAGE
Y01 DE20005	1
Y01 DE20006	3
Y01 DE30010	5
Y01 DE30011	7
Y01 DE30012	9
Y01 DE30013	11
Y01 DE40014	13
Y01 DE40015	15
N01 DE02237-04	17
N01 DE02238-06	19
N01 DE12013-05	21
N01 DE12022-05	23
N01 DE12041-03	25
N01 DE12062-06	27
N01 DE12093-05	29
N01 DE12330-04	31
N01 DE12331-04	33
N01 DE12332-03	35
N01 DE12333-03	37
N01 DE12375-07	39
N01 DE12376-04	41
N01 DE12377-06	43
N01 DE12379-06	45
N01 DE12380-04	47
N01 DE12381-03	49
N01 DE12382-04	51
N01 DE12383-06	53
N01 DE12384-03	55
N01 DE12386-04	57
N01 DE22003-05	59
N01 DE22005-04	61
N01 DE22030-05	63
N01 DE22039-03	65
N01 DE22045-01	67
N01 DE22400-02	69
N01 DE22401-01	71
N01 DE22402-02	73
N01 DE22403-02	75
N01 DE22404-02	77
N01 DE22406-01	79
N01 DE22407-02	81
N01 DE22409-02	83
N01 DE22410-02	85

IDENTIFICATION NUMBER PAGE

NO1 DE22412-02 87
NO1 DE22413-02 89
NO1 DE22414-03 91
NO1 DE22415-01 93
NO1 DE32405-01 95
NO1 DE32408-01 97
NO1 DE32416-00 99
NO1 DE32417-01 101
NO1 DE32418-01 103
NO1 DE32419-01 105
NO1 DE32420-01 107
NO1 DE32421-01 109
NO1 DE32422-01 111
NO1 DE32423-03 113
NO1 DE32424-01 115
NO1 DE32425-01 117
NO1 DE32427-01 119
NO1 DE32428-01 121
NO1 DE32429-01 123
NO1 DE32430-01 125
NO1 DE42431-01 127
NO1 DE42434-01 129
NO1 DE42435-01 131
NO1 DE42436-01 133
NO1 DE42437-01 135
NO1 DE42438-01 137
NO1 DE42439-01 139
NO1 DE42440-01 141
NO1 DE42441-01 143
NO1 DE42442-01 145
NO1 DE42443-01 147
NO1 DE42444-01 149
NO1 DE42445-01 151
NO1 DE42446-01 153
NO1 DE71475-10 155
NO1 DE71476-10 157
NO1 DE81262-07 159

INDEX

RESEARCH PROJECTS BY SUBJECT AREA

SUBJECT AREA		PAGE
ACTINOMYCES	F	9
ADHESIVE SEALANTS	D	1
ADHESIVE SEALANTS	D	15
ADHESIVE SEALANTS	D	29
ADHESIVE SEALANTS	D	27
ADHESIVE SEALANTS	D	25
ANTIBODIES	D	37
ANTIBODIES	D	73
ANTIBODIES	D	137
ANTIBODIES, VIRAL	D	73
ANTICARIES AGENTS	D	35
ANTICARIES AGENTS	D	21
ANTIGENS	D	91
ANTIMICROBIAL AGENTS	D	125
ANTIPLAQUE AGENTS	D	125
ANTIPLAQUE AGENTS	D	135
ANTIPLAQUE AGENTS	D	141
APATITES	D	103
ARACHNIA	F	9
ARECA	D	155
BABOONS	F	155
BABOONS	F	157
BABOONS	F	111
BABOONS	F	109
BACTERIA	F	83
BACTERIA	F	81
BACTERIA	F	7
BACTERIA	F	33
BACTERIA	F	35
BACTERIA	F	37
BARNACLES	F	19
BARNACLES	F	17
BEHAVIORAL SCIENCES	B	113
BETEL	D	155
BIOCHEMISTRY	B	89
BIOPSY	C	121
BIOPSY	C	3
BIOPSY	C	123
BIOPSY	C	159
BIOPSY	C	63
CALCIUM	D	3
CALCIUM	D	159
CARBON	D	157
CARCINOMA	A	155

NIDR ANNUAL REPORT - FY 74

INDEX

RESEARCH PROJECTS BY SUBJECT AREA

SUBJECT AREA		PAGE
CHEWING GUM	C	47
CHILD	F	79
CHILD	F	45
CHILD	F	69
CHILD	F	47
CHILD	F	27
CHILD	F	63
CHILD	F	25
CHILD	F	29
CHILD	F	147
CHILD	F	119
CHILD	F	85
CHILD	F	115
CHILD	F	1
CHILD	F	125
CHILD	F	113
CHLORHEXIDINE	D	61
CLINICAL TRIALS	C	25
CLINICAL TRIALS	C	21
CLINICAL TRIALS	C	27
CLINICAL TRIALS	C	29
CLINICAL TRIALS	C	35
CLINICAL TRIALS	C	41
CLINICAL TRIALS	C	45
CLINICAL TRIALS	C	39
CLINICAL TRIALS	C	79
CLINICAL TRIALS	C	69
CLINICAL TRIALS	C	47
CLINICAL TRIALS	C	119
CLINICAL TRIALS	C	125
CLINICAL TRIALS	C	85
CLINICAL TRIALS	C	117
CLINICAL TRIALS	C	149
CLINICAL TRIALS	C	151
CLINICAL TRIALS	C	147
COLLAGEN	D	11
CRYSTALLOGRAPHY	B	5
CYSTIC FIBROSIS	A	67
DENTAL CARIES	A	67
DENTAL CARIES	A	37
DENTAL CARIES	A	29
DENTAL CARIES	A	25
DENTAL CARIES	A	65
DENTAL CARIES	A	63
DENTAL CARIES	A	39
DENTAL CARIES	A	27

SUBJECT AREA		PAGE
DENTAL CARIES	A	31
DENTAL CARIES	A	61
DENTAL CARIES	A	21
DENTAL CARIES	A	59
DENTAL CARIES	A	43
DENTAL CARIES	A	51
DENTAL CARIES	A	75
DENTAL CARIES	A	55
DENTAL CARIES	A	97
DENTAL CARIES	A	49
DENTAL CARIES	A	79
DENTAL CARIES	A	77
DENTAL CARIES	A	45
DENTAL CARIES	A	99
DENTAL CARIES	A	93
DENTAL CARIES	A	87
DENTAL CARIES	A	119
DENTAL CARIES	A	113
DENTAL CARIES	A	15
DENTAI CARIES	A	1
DENTAL CARIES	A	117
DENTAL CARIES	A	115
DENTAL CARIES	A	85
DENTAL CARIES	A	147
DENTAL CARIES	A	149
DENTAL CARIES	A	129
DENTAL CARIES	A	151
DENTAL CARIES	A	137
DENTAL CEMENT	D	17
DENTAL CEMENT	D	19
DENTAL CEMENTS	D	23
DENTAL ENAMEL	E	69
DENTAL ENAMEL	E	159
DENTAL ENAMEL	E	121
DENTAL ENAMEL	E	123
DENTAL ENAMEL	E	3
DENTAL MATERIALS	D	109
DENTAL MATERIALS	D	111
DENTAL MATERIALS	D	107
DENTAL MATERIALS	D	15
DENTAL MATERIALS	D	133
DENTAL MATERIALS	D	131
DENTAL MATERIALS	D	53
DENTAL MATERIALS	D	23
DENTAL PLAQUE	A	37
DENTAL PLAQUE	A	41

SUBJECT AREA		PAGE
DENTAL PLAQUE	A	21
DENTAL PLAQUE	A	61
DENTAL PLAQUE	A	47
DENTAL PLAQUE	A	91
DENTAL PLAQUE	A	97
DENTAL PLAQUE	A	81
DENTAL PLAQUE	A	135
DENTAL PLAQUE	A	137
DENTAL PLAQUE	A	139
DENTAL PLAQUE	A	141
DENTAL PLAQUE	A	115
DENTAL PLAQUE	A	119
DENTAL PLAQUE	A	7
DENTAL PLAQUE	A	93
DEVELOPMENT	B	105
DEVELOPMENT	B	95
DEXTRANOSE	D	21
DIAGNOSIS	C	67
DIET	C	41
DIET	C	51
DIET	C	75
DIET	C	97
DIET	C	127
DIET	C	129
DIET	C	143
DIET	C	145
DNA	D	13
DOGS	F	107
ELASTIN	D	11
ELECTROCHEMISTRY	C	5
ELECTRON SPIN RESONANCE	C	103
EMBRYO	E	95
ENZYMES	D	101
ENZYMES	E	33
ENZYMES	E	31
ENZYMES	D	137
FACE	E	105
FACE	E	95
FETUS	E	95
FLUORAPATITE	D	5
FLUORESCENT ANTIBODY TECHNIC	C	9
FLUORESCENT ANTIBODY TECHNIC	C	7
FLUORESCENT ANTIBODY TECHNIC	C	83
FLUORESCENT DYES	D	117
FLUORIDATION	C	1
FLUORIDE	D	151

SUBJECT AREA		PAGE
FLUORIDE	D	3
FLUORIDE	D	159
FLUORIDE	D	149
FLUORIDE	D	153
FLUORIDE	D	69
FLUORIDE	D	63
FLUORIDE	D	39
FLUORIDE	D	45
FLUORIDES	D	123
FLUORIDES	D	121
FLUORIDES	D	119
FOOD	C	59
FOOD	C	65
FOOD	C	55
FOOD	C	99
FOOD	C	51
FOOD	C	75
GELS	D	69
GELS	D	151
GELS	D	149
GLYCEROPHOSPHATES	D	139
GLYCEROPHOSPHATES	D	63
HERPES SIMPLEX	A	73
HUMAN	F	117
HUMAN	F	77
HUMAN	F	95
HUMAN	F	91
HUMAN	F	43
HUMAN	F	49
HUMAN	F	45
HUMAN	F	39
HUMAN	F	41
HUMAN	F	21
HUMAN	F	87
HUMANS	F	139
HYDROXYAPATITE	D	5
IMMUNOLOGY	B	31
IMMUNOLOGY	B	37
IMPLANTATION	C	157
IMPLANTATION	C	107
IMPLANTATION	C	109
IMPLANTATION	C	57
IMPLANTATION	C	111
INDIANS, NORTH AMERICAN	F	1
INDIANS, SOUTH AMERICAN	F	55
INDIANS, SOUTH AMERICAN	F	59

SUBJECT AREA		PAGE
JAW	E	101
LYMPHOCYTES	E	91
METALS	D	57
MICROBIOLOGY	B	81
MICROBIOLOGY	B	33
MICROBIOLOGY	B	43
MICROBIOLOGY	B	35
MICROBIOLOGY	B	93
MICROSCOPY, ELECTRON	C	105
MINERALS	D	103
MINORITY GROUPS	F	1
MONKEYS	F	71
MONKEYS	F	97
MONKEYS	F	31
MONKEYS	F	129
MONKEYS	F	145
MONKEYS	F	143
MOUTH MUCOSA	E	145
MOUTH MUCOSA	E	143
MOUTH	E	95
MOUTHWASHES	D	39
MOUTHWASHES	D	45
MOUTHWASHES	D	139
MOUTHWASHES	D	149
MOUTHWASHES	D	119
MOUTHWASHES	D	151
MUCOUS MEMBRANE	E	13
MUSSELS	F	19
MUSSELS	F	17
PANELA	D	127
PEPTIDES	D	11
PERIODONTAL DISEASES	A	119
PERIODONTAL DISEASES	A	115
PHOSPHATES	D	103
PHOSPHATES	D	97
PHOSPHATES	D	47
PHOSPHATES	D	51
PHOSPHATES	D	159
PLASTICS	D	53
PREVENTIVE DENTISTRY	B	113
PREVENTIVE DENTISTRY	B	1
PREVENTIVE DENTISTRY	B	79
PREVENTIVE DENTISTRY	B	85
PREVENTIVE DENTISTRY	B	115
PREVENTIVE DENTISTRY	B	153
PREVENTIVE DENTISTRY	B	15

SUBJECT AREA		PAGE
PROSTHESIS	C	131
PROSTHESIS	C	133
PROTEINS	D	89
PYRIDOXINE	D	97
RADIO THERAPY	C	43
RADIOTHERAPY	C	87
RATS	F	75
RATS	F	101
RATS	F	51
RATS	F	31
RHEUMATOID FACTOR	D	73
RODENTS	F	137
ROTHIA	F	9
SALIVA	E	137
SALIVA	E	87
SALIVA	E	77
SENSATION	B	71
SOIL	B	59
SOIL	B	55
SPECTROPHOTOMETRY	C	49
SPECTROPHOTOMETRY	C	3
SPECTRUM ANALYSIS	C	11
SUCROSE	D	93
SWEETENING AGENT	D	127
SWEETENING AGENTS	D	89
SWEETENING AGENTS	D	99
TOBACCO	D	155
TOLUIDINES	D	13
TOOTH	E	49
TRACE ELEMENTS	D	49
TRACE ELEMENTS	D	55
TRANSPLANTATION	C	157
WATER	D	147
XEROSTOMIA	A	43

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	Y01 DE20005
ORGANIZATION.....	INDIAN HEALTH SERVICE, HSMHA
ADDRESS.....	ROCKVILLE MD
INITIAL START DATE.....	10-01-71
EXPIRATION DATE.....	06-30-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	BUTTS, JOHN
NIDR PROJECT OFFICER.....	THOMSON, L ARIEL
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

CLINICAL CONTROL OF SMOOTH SURFACE, PIT & FISSURE CARIES

OBJECTIVES AND WORK SCOPE:
Purpose of Project is to determine the dental caries preventive benefit of a combined program of tooth sealant and repeated fluoride application.

Two groups of American Irdian 5th and 6th graders will be randomly assigned to receive maintenance care or preventive measures with maintenance care. Both groups will have all accumulated carious lesions restored before the study commences and receive additional care as required. The Public Health significance of the preventive measures will be determined by contrasting the care required during a three year observation period to estimate the cost benefit.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	Y01 DE20006
ORGANIZATION.....	DEPARTMENT OF NAVY
ADDRESS.....	GREAT LAKES IL
INITIAL START DATE.....	10-16-71
EXPIRATION DATE.....	06-30-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	KEENE, HARRIS J
NIDR PROJECT OFFICER.....	ENGLANDER, HAROLD R
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

CALCIUM & FLUORIDE IN HUMAN TOOTH ENAMEL

OBJECTIVES AND WORK SCOPE:
To provide the personnel, equipment, and expendable supplies to provide analytical procedures per year principally to provide accurate quantification of calcium and fluoride in tooth enamel samples.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	Y01 DE30010
ORGANIZATION.....	NATIONAL BUREAU OF STANDARDS
ADDRESS.....	WASHINGTON DC
INITIAL START DATE.....	09-01-72
EXPIRATION DATE.....	06-30-74
ORGANIZATION CODE.....	INT
PROJECT DIRECTOR.....	FRANKLIN, ALAN D
NIDR PROJECT OFFICER.....	FOWLER, BRUCE O
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

MASS TRANSPORT & PHYSICAL PROPERTIES OF CALCIUM APATITES

OBJECTIVES AND WORK SCOPE:

Prepare and furnish to NIDR large single crystals of pure hydroxyapatite, $Ca_5(PO_4)_3OH$. These crystals are to be prepared from fluorapatite using electrochemical techniques to be developed by the Bureau. They are to be approximately one millimeter thick in the crystallographic c - axis direction and have lateral dimensions in both crystallographic a - axis directions of the order of a centimeter.

Contingent upon satisfactory preparation of pure crystals, the Bureau shall determine the OH^- diffusion coefficients, the ionic conductivity, and the OH^- transference numbers of hydroxyapatite as a function of temperature and crystallographic direction.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	Y01 DE30011
ORGANIZATION.....	CENTER FOR DISEASE CONTROL, HSMHA
ADDRESS.....	ATLANTA GA
INITIAL START DATE.....	11-01-72
EXPIRATION DATE.....	06-30-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	CHERRY, WILLIAM B
NIDR PROJECT OFFICER.....	THOMSON, L ARIEL
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

DEVELOPMENT OF SPECIFIC FLUORESCENT ANTIBODY REAGENTS

OBJECTIVES AND WORK SCOPE:
CDC shall provide the personnel, equipment, and expendable supplies to conduct a research project to: (1) develop, evaluate, and improve to "reagent quality" FA conjugates designed to be specific for certain plaque organisms considered important in dental caries etiology (e.g., Streptococcus mutans, serotypes a-e); (2) research improved methods for preparing reagent conjugates specific for plaque organisms; and (3) determine and recommend optimal conditions for the utilization of FA conjugates in identifying plaque bacteria.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	Y01 DE30012
ORGANIZATION.....	CENTER FOR DISEASE CONTROL, HSMHA
ADDRESS.....	ATLANTA GA
INITIAL START DATE.....	11-01-72
EXPIRATION DATE.....	06-30-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	PICKARD, LUCILLE G
NIDR PROJECT OFFICER.....	HAGEAGE, GEORGE J
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

FLUORESCENT ANTIBODY REAGENTS FOR FILAMENTOUS ORGANISMS

OBJECTIVES AND WORK SCOPE:

CDC shall provide the personnel, equipment, and expendable supplies to conduct a research project to: (1) develop and evaluate specific FA conjugates for A. viscosus serotypes 1 and 2, A. naeslundii serotype 2, A. odontolyticus, Arachnia propionica serotypes 1 and 2, and Rothia dentocariosa; (2) define the optimal conditions for the application of these conjugates; and (3) formulate protocols to be followed for the large-scale production of the approved conjugates.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	Y01 DE30013
ORGANIZATION.....	NATIONAL BUREAU OF STANDARDS
ADDRESS.....	WASHINGTON DC
INITIAL START DATE.....	04-01-73
EXPIRATION DATE.....	06-30-74
ORGANIZATION CODE.....	INT
PROJECT DIRECTOR.....	TORCHIA, DENNIS A
NIDR PROJECT OFFICER.....	MARTIN, GEORGE R
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

AN NMR STUDY OF COLLAGEN ELASTIN & RELATED PEPTIDES

OBJECTIVES AND WORK SCOPE:

It is proposed to examine the structure of collagen, peptides derived from collagen as well as elastin by 13_C and conventional NMR spectroscopy by examining the spectrum of native and randomly coiled proteins to determine the orientation of given amino acids in the protein. Both collagen and small peptides from collagen will be studied. In the latter case it is possible to obtain a small peptide (a1-CB1, 35 amino acids) in a random structure or a triple helical, collagen-like structure. The orientation of every side chain in the collagen-like structure of a1-CB1 can be solved by NMR spectroscopy. These findings can be extended to the collagen molecule.

Similar studies can be made on elastin to probe its structure.

SALIENT RESULTS TO DATE:

Carbon-13 spectra of calf ligamentum nechae have been measured as a function of swelling agent, temperature and fiber elongation. Relaxation times obtained from these spectra indicate that the polypeptide backbone carbons undergo rapid rotational motion characterized by correlation times ca. 10^{-8} sec. when the ligament is swollen by aqueous saline. Raising the temperature, swelling the fiber with ethanol-water or 2M KCNS solutions produce small reductions in the correlation times while extending the fiber (up to 25%) has no measurable effect on chain mobility. Taken together, these results indicate that elastin chains are highly flexible in the physiological environment and hence that their elasticity results, in part, from chain configurational entropy.

Spectra of the rat skin collagen fragment a1-CB2, obtained at 3° and 32° C show marked differences in line width and relaxation times corresponding to the helical (T=3° C) and random coil (T=32° C) states. A comparison of relaxation times obtained at the two temperatures confirms that the backbone is flexible at 32° but rigid at 3°. Furthermore, differences in spectral properties of sidechain resonances in the helix indicate that some sidechains participate in strong intramolecular interactions. A detailed analysis of this data is currently underway and should indicate which residues most strongly influence helix stability.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	Y01 DE40014
ORGANIZATION.....	VETERANS ADMINISTRATION HOSPITAL
ADDRESS.....	EAST ORANGE NJ
INITIAL START DATE.....	01-01-74
EXPIRATION DATE.....	06-30-74
ORGANIZATION CODE.....	EXP
PROJECT DIRECTOR.....	MASHBERG, ARTHUR
NIDR PROJECT OFFICER.....	HAYES, RICHARD L
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

TECHNIQUES FOR EARLY DETECTION OF ORAL CARCINOMA

OBJECTIVES AND WORK SCOPE:

A study to develop and evaluate clinical criteria for the early detection of oral carcinoma and to evaluate toluidine blue and a DNA-acridine binding test as techniques for detection of clinically inapparent carcinoma and as techniques for identifying patients with precancerous field alterations of the oral mucosa.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	Y01 DE40015
ORGANIZATION.....	NATIONAL BUREAU OF STANDARDS
ADDRESS.....	WASHINGTON DC
INITIAL START DATE.....	07-01-73
EXPIRATION DATE.....	06-30-74
ORGANIZATION CODE.....	EXP
PROJECT DIRECTOR.....	CASSEL, JAMES M
NIDR PROJECT OFFICER.....	KAKEHASHI, SAMUEL
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

INTERACTIONS OF ORAL STRUCTURES & RESTORATIVE MATERIALS

OBJECTIVES AND WORK SCOPE:

The study is being performed to obtain new knowledge on the properties and interactions of oral structures and restorative materials. The subject matter to be explored and studied, including subtasks, is as follows:

1. Adhesion of Restorative and Caries-Preventive Materials to Tooth Surfaces
   - A. Surface Characterization of Dental Materials by Water Adsorption
   - B. Novel Approach to Development and Assessment of Adhesion in Dental Materials
   - C. Synthesis for Improved Adhesion and Stability of Composite Restorative and Sealant Materials
   - D. Polymer Grafting, a Technique for Bonding to Mineralized Collagen Surfaces

2. Physical, Mechanical and Physicochemical Properties of Hard and Soft Tissues of Dental Materials
   - A. Dimensional Changes in Tooth Structure
   - B. Wear-Resistance of Dental Restorative Materials
   - C. Zinc-Polycarboxylate Dental Cement, Properties and Technique for Improvement

SALIENT RESULTS TO DATE:

In general, it was found that the thermal expansion phenomena in bone are similar to those of dentin. The significance of these studies is to relate the dimensional changes of restorative materials to those of the tooth. A device has been designed and fabricated for measuring accurately the degree of wear to be expedted from composites and other restorative materials, without the need for long term clinical observation. It was found that the compressive strength of composite carboxylate cements containing potassium titanate as a reinforcing agent is doubled, and tensile strength increased 2 1/2 times. Improved interfacial bonding between fillers and matrices may provide better dental cements than are now available.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE02237-04
ORGANIZATION.....	BATTELLE MEMORIAL INSTITUTE
ADDRESS.....	COLUMBUS OH
INITIAL START DATE.....	06-26-70
EXPIRATION DATE.....	08-25-73
ORGANIZATION CODE.....	EXP
PROJECT DIRECTOR.....	HILLMAN, ROBERT E
NIDR PROJECT OFFICER.....	KAKEHASHI, SAMUEL
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

STUDY OF ADHESIVE MECHANISM OF THE SEA MUSSEL

OBJECTIVES AND WORK SCOPE:

The workscope of the existing contract was amended as follows. The Contractor shall maintain mussel and barnacle colonies. The cement and/or its components shall be chemically and physically identified before secretion, immediately after secretion, and after aged cement has been attached for periods of time. After the components of the cement which are critical to hardening and adhesion in the aqueous environment have been defined and purified, the Contractor shall synthesize products having similar adhesive properties which will be used for dental research. The Contractor shall furnish quantities of cement(s) to the Government for testing at regular intervals when they believe they have a cementitious product ready for dental testing.

SALIENT RESULTS TO DATE:

Colonies of both Mytilus edulis and M. californianus continue to be maintained at both the Duxbury and Columbus facilities. Work was primarily aimed at further characterization of the adhesive secretion. Material was collected from the mussels in the usual manner. The protein components of M. edulis were completely excluded from Sephadex G-50 and G-75, indicating the molecular weight above 30,000. Protein was eluted at pH2 from DEAE-Sephadex at 1 M NaCL and above, indicating binding to the dextran through the acidic aspartate and glutamate residues. Two major fractions absorbing at 208mm can be obtained, only one of which is retained upon dialysis. Electrophoresis is currently being carried out on this fraction. Electrophoresis of secretions from both species show a small portion of the material remaining at the origin, with a large amount of material migrating toward the anode. This fraction may contain the large proportion of glutamate and aspartate residues.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE02238-06
ORGANIZATION.....	FRANKLIN INSTITUTE
ADDRESS.....	PHILADELPHIA PA
INITIAL START DATE.....	06-26-70
EXPIRATION DATE.....	07-31-74
ORGANIZATION CODE.....	EXP
PROJECT DIRECTOR.....	THELEN, EDWARD
NIDR PROJECT OFFICER.....	KAKEHASHI, SAMUEL
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

STUDY OF ADHESIVE MECHANISM DIFFERENT SPECIES SEA MUSSEL

OBJECTIVES AND WORK SCOPE:

Independently and not as an agent of the Government, the Contractor shall exert its best efforts to determine the chemical and physical properties of the cementum of marine organisms including the mussel and barnacle in both the hardened and unhardened state, for use in synthesizing similar products which will be useful in dentistry. The Contractor shall also maintain mussel and barnacle colonies and other organisms as required by the study. The Contractor shall furnish small quantities of cement(s) to the Government for testing at regular intervals when they believe they have a cementitious product ready for dental testing.

SALIENT RESULTS TO DATE:

Work so far has shown that byssus is a crosslinked protein. Solutions derived from arca byssus are characterized by a distinct yellow color and by marked fluorescence. These features are also observed in elastin. It is possible, therefore, that the material contains some of the crosslinks found in elastin. These include the desmosines and the isodesomines which have characterisitc U.V. absorption and can be isolated by ion exchange. It appears byssus in not homogeneous. Loose filaments lying between fivers may represent the water soluble fraction whose function could be to cement the fibers into sheets.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12013-05
ORGANIZATION.....	UNIVERSITY OF MIAMI
ADDRESS.....	CORAL GABLES FL
INITIAL START DATE.....	08-15-70
EXPIRATION DATE.....	08-14-73
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	ZINNER, DORAN D
NIDR PROJECT OFFICER.....	SENNING, RICKLEY S
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

STUDIES OF ANTICARIES AGENTS

OBJECTIVES AND WORK SCOPE:

Contractor shall provide the necessary staff, facilities and populations to conduct clinical studies of potential anti-caries agents encompassing the following objectives: To test the hypothesis that certain strains of dextran-forming streptococci are etiologically involved in the induction of human dental caries; To study the feasibility of the use of the enzyme dextranase as an anti-plaque and caries-inhibitory agent in humans; To study the effect of long-term use of dextranase on the oral streptococcal flora; To study the effect of long-term use of dextranase on gingival status.

SALIENT RESULTS TO DATE:

Baseline examiniations, daily treatment regimens with test enzyme, and year-end examinations are complete for the approximately 500 participants. Microbiologic analyses of plaque specimens from every subject are nearing completion. Analyses of clinical data will take place later this year.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12022-05
ORGANIZATION.....	UNIVERSITY OF UTAH
ADDRESS.....	SALT LAKE CITY UT
INITIAL START DATE.....	11-17-70
EXPIRATION DATE.....	08-16-73
ORGANIZATION CODE.....	EXP
PROJECT DIRECTOR.....	WILLIAMS, M L
NIDR PROJECT OFFICER.....	KAKEHASHI, SAMUEL
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

ENGINEERING EVALUATION OF DENTAL ADHESIVES

OBJECTIVES AND WORK SCOPE:

The Contractor shall concentrate its efforts in providing a significantly large sample size, including statistical evaluation, of the "blister test" to establish its reproducibility as a test method for dental application, as well as for a comparison to other adhesive test methods.

SALIENT RESULTS TO DATE:

This group showed that the two new tests were indeed superior to other tests for studying dental adhesives. Their data from the new tests are more reliable and quantitative than those from other commonly used tests. They noted that the necessary materials for the "blister" test can be obtained for less than $100.00. The adhesive strength and other physical properties of barnacle cement have been determined in a cooperative study with the Navy Research Laboratory at Mare Island, California. A few commercial dental adhesives have also been evaluated. Good progress has been made during the first year. They have proved the feasibility of these tests for studying dental adhesives.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12041-03
ORGANIZATION.....	HOWARD UNIVERSITY
ADDRESS.....	WASHINGTON DC
INITIAL START DATE.....	11-25-70
EXPIRATION DATE.....	01-24-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	SONI, NADAR
NIDR PROJECT OFFICER.....	STILES, HORACE M
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

ADHESIVE SEALANT MATERIAL PREVENTION PIT FISSURE CARIES

OBJECTIVES AND WORK SCOPE:

Approximately 1,000 children between the ages of 6 and 14 will have one or more sites of contralaterally matched teeth covered with an adhesive sealant material. These sites will be observed and examined over a period of four years to assess the durability of the sealant material, the caries preventive ability of the sealant material, the fate of the tooth site in the event of sealant loss, whether dental hygienists can effectively apply the sealant under the supervision of a dentist, and the time and difficulties involved in applying the material in field-clinical conditions.

SALIENT RESULTS TO DATE:

Of the 1,000 children, 913 have received sealant material in one or more sites on one of a pair of contralaterally matched teeth. These placements were begun in November, 1960, and completed in February, 1970. The first six month examinations were completed and submitted to the NIDR, where they were processed and analyzed. Since the sealant placement extended over a period of four months, the six month evaluations follow the same schedule. The one year evaluations and examinations are currently in progress. The results of the six month examinations show that the adhesive sealant remained in place (either partially or completely) in over 38% of the treated sites. No significant differences were noted in the incidence of dental caries between the experimentally treated sites and the contralaterally matched untreated control sites.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12062-06
ORGANIZATION.....	UNIVERSITY OF PUERTO RICO
ADDRESS.....	SAN JUAN
INITIAL START DATE.....	12-30-70
EXPIRATION DATE.....	01-31-75
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	HARRIS, NORMAN O
NIDR PROJECT OFFICER.....	FREW, RALPH A
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

EVALUATION OF AN ADHESIVE SEALANT MATERIAL

OBJECTIVES AND WORK SCOPE:

This project is designed to evaluate the anticaries potential of an adhesive sealant in a dental public health program. The sealant is placed in children's teeth by various types of dental auxiliary personnel under a variety of field conditions in the Virgin Islands. Baseline and follow up examinations will define the efficacy and persistance of the agent under the operant conditions. The project is entering its third year. The first year involved baseline examinations and treatment of the study population. The activity for subsequent years is primarily involved with the reexamination of the study population.

SALIENT RESULTS TO DATE:

The treatment phase of the program began in the spring of 1971 and was completed during the spring of 1972, and the first followup examination were conducted. Data from these examinations reflecting 6 months to one year's experience have been processed. Retention rates of from 30% to 80% depending on individual applying the material, type of site sealed and location of the site were found. The second followup examination reflecting 18 to 24 months experience was completed during the previous year (1973). Retention rates decreased from 10% to 30% by site from the first year's retention rates. Caries reductions approximated the retention rates for most sites.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12093-05
ORGANIZATION.....	HEALTH RESEARCH, INC
ADDRESS.....	ALBANY NY
INITIAL START DATE.....	05-17-71
EXPIRATION DATE.....	10-30-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	CONS, NAHAM C
NIDR PROJECT OFFICER.....	FREW, RALPH A
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

ADHESIVE SEALANT FIELD TRIAL

OBJECTIVES AND WORK SCOPE:

The workscope remains the same, except that portion dealing with tests on 100 children using fiberoptics has been deleted, i.e., item 6 of the Description of Work.

SALIENT RESULTS TO DATE:

Following a small pilot study in May 1971, baseline examinations were conducted in the fall of 1971, and 1,965 children had sealant applied to their teeth during the winter of 1971 and early spring of 1972. The first follow-up examination was conducted in the fall of 1972 and annual reexaminations are scheduled for the next two years. The first follow-up examination of the sealed sites and their lateral controls was computed during October-November 1972. The data forms are being processed by NIDR. Preliminary tabulations indicate a retention rate for the material of over 70%. The effect on caries experience is not great at this point, despite the good retention rate due to the low caries increment in control sites.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12330-04
ORGANIZATION.....	SOUTHERN ILLINOIS UNIVERSITY
ADDRESS.....	EDWARDSVILLE IL
INITIAL START DATE.....	06-30-71
EXPIRATION DATE.....	11-30-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	BAHN, ARTHUR N
NIDR PROJECT OFFICER.....	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

IMMUNIZATION WITH ENZYMES FROM CARIOGENIC STREPTOCCI

OBJECTIVES AND WORK SCOPE:

Contractor will exert best efforts to isolate and purify dextransucrases, levansucrases, and glycosidic hydrolases, from cariogenic streptococci, which will be investigated for their effectiveness as immunizing agents to reduce experimental dental caries.

SALIENT RESULTS TO DATE:

Two rat experiments, completion of one monkey experiment and initiation of a second monkey experiment were undertaken during the second contract year. A highly purified levansucrase injected into rats showed reduction in caries only if injected at weekly intervals. A glycosidic hydrolase preparation injected into rats elicited high-titered antibody neuraminidase. Reductions in radiographically-detectable and clinical caries were obtained in monkeys. No apparent pathological changes were observed in the monkeys. The second monkey experiment has been designed to test all three enzyme groups as anti-caries immunogens. Highly painstaking and detailed investigations have been involved in the current year of the contract but progress has been excellent.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12331-04
ORGANIZATION.....	UNIVERSITY OF MINNESOTA
ADDRESS.....	MINNEAPOLIS MN
INITIAL START DATE.....	06-29-71
EXPIRATION DATE.....	12-28-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	SCHACHTELE, CHARLES
NIDR PROJECT OFFICER.....	ROUSSOS, GERASSIMOS
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

ANTIMICROBIAL AGENTS AFFECTING CARIOGENIC MICROORGANISMS

OBJECTIVES AND WORK SCOPE:

Contractor will exert best efforts to investigate unique features of the membrane-associated phosphotransferase sugar uptake system of oral cariogenic bacteria and to analyze for antimicrobials which could inhibit this system.

SALIENT RESULTS TO DATE:

Membranes prepared from decryptified S. mutans cells have been found to contain a constitutive glucose transport system that is absolutely dependent on PEP. The membrane preparations do not possess dextral or levan sucrose activity. The membrane glucose transport system of four strains of S. mutans and eight other oral microorganisms was found to be similar and their activity was compared. In each case, PEP is used to phosphorylate the C-6 position of glucose in a reaction that is insensitive to fairly high concentration of fluoride. However, PEP production by enolase, an intracellular enzyme, is blocked by this enzyme. Several sugars, including glucose-6-P and glucose-1-P, have been found markedly to inhibit the phosphotransferase system. Two new procedures have been worked out that will allow the research to proceed more rapidly. The first of these is a preparation of active membranes by toluene treatment rather than freeze-drying: the second is an assay for enzymatically phosphorylated sugars by adsorption to DEAE-cellulose discs which are washed, dried, and radio assayed. Work on the fructose transport system and on the inhibition of sugar transport is continuing.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12332-03
ORGANIZATION.....	MEDICAL COLLEGE OF GEORGIA
ADDRESS.....	AUGUSTA GA
INITIAL START DATE.....	06-29-71
EXPIRATION DATE.....	06-28-75
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	BURNETT, GEORGE W
NIDR PROJECT OFFICER.....	SHERN, ROALD J
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

TESTS OF ANTICARIES EFFICACY OF CERTAIN AGENTS

OBJECTIVES AND WORK SCOPE:

Contractor will exert its best efforts to search for and obtain potential anticaries agents from pharmaceutical companies and conduct in vitro and in vivo tests of the anticaries efficacy of these agents.

SALIENT RESULTS TO DATE:

In the past year, the additional studies were done so that about 60 compounds have been screened in the past two years. They have identified 11 compounds which warrant further investigation. Of these, at least two will be tested in short term clinical trials.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12333-03
ORGANIZATION.....	FORSYTH DENTAL CENTER
ADDRESS.....	BOSTON MA
INITIAL START DATE.....	06-28-71
EXPIRATION DATE.....	06-27-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	TAUBMAN, MARTIN A
NIDR PROJECT OFFICER.....	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

LOCAL IMMUNIZATION EFFECT EXPERIMENTAL CARIES

OBJECTIVES AND WORK SCOPE:

Contractor will exert best efforts to investigate the effects of specifically induced salivary antibody to Streptococcus mutans upon plaque bacteria and dental caries in gnotobiotic rats and conventional hamsters.

SALIENT RESULTS TO DATE:

Experiments were initiated in germfree rats to determine effective modes of immunization producing a salivary antibody response. These experiments have recently been completed and the results are being tabulated. Polyvalent rabbit antisera to hamster serum and whole saliva are being prepared. Immunochemically pure hamster lgG was isolated from serum by chromatography on DEAE-cellulose.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12375-07
ORGANIZATION.....	FORSYTH DENTAL CENTER
ADDRESS.....	BOSTON MA
INITIAL START DATE.....	06-28-71
EXPIRATION DATE.....	12-31-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	DE PAOLA, PAUL F
NIDR PROJECT OFFICER.....	JOLY, OLGA
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

TOPICAL USE OF ACIDIFIED NH4F VS. ACIDIFIED NAF

OBJECTIVES AND WORK SCOPE:

The Contractor will compare the relative caries inhibitory effect of supervised, daily, one-minute mouth rinses in school with 5 ml of NH4F, pH4.4 containing 5 mg of F ion, and determine fluoride uptake in subjects receiving the foregoing treatments and to relate fluoride uptake to caries experience on a group basis.

SALIENT RESULTS TO DATE:

Completion of the third semi-annual topical applications. Completion of 12-month follow-up clinical and radiographic examinations. Clinical and biopsy data are currently being processed. No caries protection has, as yet, become apparent in either of the test groups. However, because of the slow rate of development and progression of dental caries, field clinical trials are usually conducted for a minimum of two years. Progress has been satisfactory and proceeds according to protocol.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12376-04
ORGANIZATION.....	UNIVERSITY OF MINNESOTA
ADDRESS.....	MINNEAPOLIS MN
INITIAL START DATE.....	06-30-71
EXPIRATION DATE.....	06-29-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	FOLKE, LARS E A
NIDR PROJECT OFFICER.....	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

INFLUENCE MODIFIED DIETS HUMAN PLAQUE & ORAL TISSUES

OBJECTIVES AND WORK SCOPE:

The scope and nature of this clinical research study is directed toward achieving the following objectives: 1. The development of a precise clinical method or procedure for evaluating the effects of diet variations upon microbial and biochemical composition of human dental plaque. 2. The estimation of the relative effects of sucrose upon plaque formation in human subjects. 3 The measurement of effects of sodium trimetaphosphate upon plaque formation in the presence as well as the absence of sucrose.

SALIENT RESULTS TO DATE:

The early portion of this contract year was spent in development of new analytical methods, refinement and extensions of current methods in the microbiological and biochemical analysis of plaque. These methods have confirmed the validity of bacterial speciation and quantitation and biochemical characterization of plaque from the two-week diet periods. In vitro TMP studies have shown incidental inhibition of streptococcal growth, no effect on growth rates, and inhibition of pH reduction of acids. TMP is not hydrolyzed by most oral streptococci. In the presence of TMP, a possible increase of soluble polysaccharide synthesis was shown by Str. mutans BHT and GS5. A method of studying the cariogenic potential of fissure plaque has been developed. This device will test, in vivo, various parameters which have been studied with smooth surface plaque. The Principal Investigator is making satisfactory progress and will probably achieve major goals for the second contract year if the clinical trials with dietary TMP can get underway during the fourth quarter.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12377-06
ORGANIZATION.....	UNIVERSITY OF TEXAS AT HOUSTON
ADDRESS.....	HOUSTON TX
INITIAL START DATE.....	06-30-71
EXPIRATION DATE.....	12-29-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	DREIZEN, SAMUEL
NIDR PROJECT OFFICER.....	STILES, HORACE M
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

EFFECT OF XEROSTOMIA ON HUMAN ORAL MICROFLORA

OBJECTIVES AND WORK SCOPE:

Prime objectives are: 1. Clarify the saliva-microbial-dental caries relationship by: a. Delineating the general characteristics of the oral microbial population changes in patients with radiation induced xerostomia b. Identifying the specific changes in the occurrence and numbers of those microorganisms which have been implicated in the caries process. c. Elucidating the effect of caries preventive agents and procedures on the oral microflora in patients with radiation induced xerostomia. 2. Establish a human model system for the rapid screening of anticaries agents in the presence of unusually potent caries challenge. Determine the fluoride level in plaque in individuals studied at time of postradition. Determine titrations of total acidity produced by the plaque suspensions. Analyze the lactate produced by the suspensions and specific microbial isolates. Place remaining entering study subjects on sucrose free diet. During the first 6-8 weeks of regimen, plaque specimens shall be monitored at 2-week intervals.

SALIENT RESULTS TO DATE:

The number of patients originally proposed for this study was 25; however, that number has had to be increased to 30 at the present time (with more inclusions expected) to balance the fluoride non-fluoride groups and to compensate for patient loss due to death or other circumstances. In the surviving 21 patients under study, all developed xerostomia as expected within two to three weeks following initiation of radiation therapy; furthermore, this has been accompanied by a change to a "highly" cariogenic oral microflora. There has been a striking difference in the incidence of postradiation caries between the fluoride non-fluoride groups. The eleven patients in the non-fluoride group (77 postradiation patient months) have demonstrated 195 new carious surfaces, while the seven patients in the fluoride group (39 postradiation patient months) have demonstrated only two new carious surfaces.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12379-06
ORGANIZATION.....	FORSYTH DENTAL CENTER
ADDRESS.....	BOSTON MA
INITIAL START DATE.....	06-28-71
EXPIRATION DATE.....	12-31-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	DE PAOLA, PAUL F
NIDR PROJECT OFFICER.....	JOLY, OLGA
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

NH4F MOUTH RINSE VERSUS HIGH-POTENCY FLUORIDE RINSE

OBJECTIVES AND WORK SCOPE:

To quantify plaque and gingival conditions, the clinical examinations will also include the Green and Vermillion and the Russell Periodontal Index. This information will be correlated with the other measurements obtained in the study.

SALIENT RESULTS TO DATE:

Mouth rinses continued during school days. Twelve-month follow-up clinical, radiographic, and biopsy procedures were completed. DMFS and biopsy data are currently being statistically evaluated. The data shows a moderate reduction of caries increments in the test groups. However, because of the slow rate of development and progression of dental caries, field clinical trials are usually conducted for a minimum of two years. Progress is satisfactory and proceeding as per protocol.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12380-04
ORGANIZATION.....	UNIVERSITY OF ALABAMA
ADDRESS.....	BIRMINGHAM AL
INITIAL START DATE.....	06-28-71
EXPIRATION DATE.....	12-27-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	FINN, SIDNEY
NIDR PROJECT OFFICER.....	FREW, RALPH A
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

STUDY OF TRIMETAPHOSPHATE ON PLAQUE

OBJECTIVES AND WORK SCOPE:

Objective of study is to establish and measure anticaries activity of Sodium Trimetaphosphate (STMP) when topically applied to the dentition of children in a chewing gum vehicle. The gum will be distributed to approximately 600 children participants on a systematic basis with oral examinations to be conducted prior to the study and at 6 month intervals thereafter. Both clinical and radiographic results will be observed and recorded by the Contractor, and transmitted to NIDR for processing and analysis of the data in-house. All children will receive a dental prophylaxis prior to each examination.

SALIENT RESULTS TO DATE:

Supplying and dispensing of the gum during the school and vacation periods, supervising the chewing periods during school, and providing the required clinical and radiographic examinations for each child has been accomplished by the contractor during the previous year. Caries increments do not show significant differences between groups but treatment had been in effect for less than one year, and the increment found was not large. The microbiological examinations have failed to detect differences between study groups and this phase will be eliminated from the study unless the May, 1973, examinations show significant differences.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12381-03
ORGANIZATION.....	EASTMAN DENTAL CENTER
ADDRESS.....	ROCHESTER NY
INITIAL START DATE.....	06-29-71
EXPIRATION DATE.....	06-28-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	LOSEE, FRED L
NIDR PROJECT OFFICER.....	JOLY, OLGA
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

TRACE ELEMENTS CONTENT OF TEETH & CARIES SUSCEPTIBILITY

OBJECTIVES AND WORK SCOPE:

Contractor will attempt to relate trace elements of teeth to their caries susceptibility by: 1. Selecting human teeth from geographic areas of high and low caries prevalence to determine the approximate concentrations in enamel and dentin of the major trace elements, together with calcium and phosphorus. 2. Analyses from residents of Colorado, Texas, New York, Ohio, Maine, and California will be reported. 3. Sufficient samples will be analyzed to provide information on intra-tissue distribution of elements so that a relationship can be established between trace element composition and resistance to caries. The following was added to the existing Scope of Work: Compare dietary factors with the trace element contents of teeth obtained from areas of high or low caries prevalence. Food, water, and other environmental sources of trace elements will be collected from areas where a dietary reconnaissance visit is made. Analysis of the trace element contents of these samples will be performed.

SALIENT RESULTS TO DATE:

Established workable procedure for obtaining bicuspids was established. Data received with the tooth includes the DMFT status, age, sex, and water supply of the individual contributing the tooth. Critical examination of the enamel to be sampled was determined to be extremely important. It was found that with the inclusion of altered, stained (after pumice prophylaxis), or carious enamel would increase the concentration of several elements depending on the proportion of included sample. The F and Sr levels in enamel and dentin are both associated with the levels found in the water supplies. Fluoride and zinc concentrations are greatest in the surface enamel, whereas SR tends to be evenly distributed. Spark-source mass spectrographic technique appears to be a desirable means to look for 74 elements in a sample of only 1 mg. By using the Laser for excitation to present a plume of evaporated material to standard electric-arc emission spectrophotometry, it was shown that teeth from two different locations in California had differences in the enamels compositions of Al, Ag, Ba, Be, Cr, Cu, Ni, Pb, Sn, and Zn. A method for the determination of density has been worked out for enamel samples weighing 10 to 120 mg.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12382-04
ORGANIZATION.....	HARVARD UNIVERSITY
ADDRESS.....	CAMBRIDGE MA
INITIAL START DATE.....	06-29-71
EXPIRATION DATE.....	06-28-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	SHAW, JAMES H
NIDR PROJECT OFFICER.....	ROGERS, WILLIAM E
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

ROLE OF FOOD IN INHIBITING CARIES

OBJECTIVES AND WORK SCOPE:

Contractor will exert best efforts to estimate caries-producing potentials of human foods and their potential role as caries or possible caries-inhibiting agents by assays with experimental rodents. Contractor will: Develop in rodents an assay which will utilize programmed feeder technique to measure caries-producing potential of human foods. Utilize assay to estimate caries-producing potentials of commonly used human foodstuffs. Evaluate efficacy of adding to foodstuffs with high caries potential, agents believed to be caries inhibitors, such as socium trimetaphosphate, calcium sucrose phosphate, and any others which may eventually be utilized in human diets. The following was added to the existing Scope of Work: Evaluate the caries-producing potential in rodents of no more than five dietary products as may be provided to the Contractor by the Government.

SALIENT RESULTS TO DATE:

Ten experiments have been completed and three additional ones are underway. In the course of these experiments, two types of assay with rodents have been developed and are being used to evaluate the relative caries-producing potential of human foods. The first type of assay is conducted in periodic feeding cages where the experimental rats are offered four meals of one-hour duration of a control diet of high nutritional quality (2700-S) and low caries-producing ability in each 24-hour period; in addition, the test substance is offered for four one-hour intervals alternating with the control diet. In the other type of assay, the control diet 2700-S and the test substance are alternated on a day-night basis in regular cages. All food items are compared with the caries-producing ability of granulated sugar (sucrose). The breakfast cereal, sugar frosted flakes, proved to have about two-thirds the caries-producing capacity of sugar. In one experiment, when sugar frosted flakes were moistened with whole milk, the mixture appeared to be less cariogenic than in the dry form. However, in two other experiments, wetting with whole milk or the incorporation of an equivalent amount of dried whole milk did not alter the caries-producing ability. Vanilla wafers, ginger snaps, and chocolate chip cookies were somewhat less cariogenic than sugar frosted flakes. Wheaties and graham crackers were still less cariogenic. Soda crackers gave little or no evidence of being able to support the caries process in these assays.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12383-06
ORGANIZATION.....	MIDWEST RESEARCH INSTITUTE
ADDRESS.....	KANSAS CITY MO
INITIAL START DATE.....	06-30-71
EXPIRATION DATE.....	06-29-74
ORGANIZATION CODE.....	EXP
PROJECT DIRECTOR.....	BREED, L W
NIDR PROJECT OFFICER.....	KAKEHASHI, SAMUEL
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

STUDY OF ELASTOMERIC LINERS FOR DENTAL RESTORATIONS

OBJECTIVES AND WORK SCOPE:

The Contractor shall screen various experimental polymers as dental restorative materials potentially useful as elastomeric liners or as composite filling bases capable of adhering to dentin and enamel. Optimal polymers as judged by in vitro adhesion tests shall be selected for in vivo testing in animals. Several polymer systems shall be tested in rats and in the teeth of dogs for the purpose of establishing toxic reactions, adhesive qualitites, marginal penetration, pulp reactions, and stability under oral conditions. In vivo results shall be correlated with in vitro tests.

SALIENT RESULTS TO DATE:

The objective of the work has been to develop an acrylate-based formulation, which upon curing, has elastomeric properties, forms a coherent bond with tooth structure and dental restorative materials, and functions as a restorative liner. In vitro and in vivo screening of several formulations by the University of Missouri at Kansas City School of Dentistry revealed little or no marginal penetration in lined restorations and controls. Retention for both the lined restorations and the controls was good. Photographic evidence showed the presence of the liner between the cavity and the restoration and separation of the restoration from the cavity in unlined specimens. In the development of these formulations by Midwest Research Institute, in vitro tests for tensile strength of adhesion demonstrated poor adhesion for liner formulations modified with chelating polymers, and these formulations were abandoned. However, a number of formulations of the base elastomeric resins provided tensile strengths of adhesion of 1000 lb/in2 or more on phosphoric acid etched dentin. Compositional parameters in the restoration systems, which were important in determining the tensile strength of adhesion, included the crosslinking monomer, the initiator system, the commercial restorative used with the liner, and the application procedure.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12384-03
ORGANIZATION.....	FORSYTH DENTAL CENTER
ADDRESS.....	BOSTON MA
INITIAL START DATE.....	06-28-71
EXPIRATION DATE.....	03-27-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	GLASS, ROBERT L
NIDR PROJECT OFFICER.....	JOLY, OLGA
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

ANALYSIS FOR TRACE METAL IN SAMPLES FROM COLOMBIA, S A

OBJECTIVES AND WORK SCOPE:

Contractor will analyze for presence of various trace elements samples obtained from two groups of people having marked differences in caries prevalence not due to fluoride. He will attempt to associate presence of these elements with resistance to caries to determine if certain trace elements in diet may potentiate anti-cariogenic effect of fluoride. Select for analysis samples of water, soil, food, saliva, and teeth which have been obtained from Colombia, S. A. Analyze these samples for presence of as many of the major trace elements as possible. Relate these elements to caries prevalence in these two communities. The existing workscope is amended to add: Conduct a nutritional survey of the populations from Heliconia and Don Matias in order to establish the dietary intake of various trace elements and other nutrients in the population of these two communities; Examine the association of the dietary intake of these elements with differences in the caries prevalence in these communities.

SALIENT RESULTS TO DATE:

All samples intended for analyses for trace metals have been completed or are in progress. Spectroscopic analyses are in progress for 25 teeth, the last of those available. Initial findings from the analyses of the first series of teeth show higher levels of manganese in teeth from the village with the higher caries prevalence. Lower mean levels of manganese were observed in teeth from the low caries village. Concentrations of iron were higher in the teeth from the low caries village. Spectroscopic analyses of the last samples of food and saliva have just been completed and the findings are being summarized. Brief summaries of data from those food samples first completed do not show the clear cut differences observed in samples of water and soil. this suggests that the source of the trace metal effect, whatever it may be, might be drinking water. The results of analyses continue to reveal definite differences in the environment of trace metals between these two villages. Except for the foods, differences are obvious in the various samples collected for analyses.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE12386-04
ORGANIZATION.....	BATTELLE PACIFIC NORTHWEST LABORATORIES
ADDRESS.....	RICHLAND WA
INITIAL START DATE.....	06-30-71
EXPIRATION DATE.....	08-31-74
ORGANIZATION CODE.....	EXP
PROJECT DIRECTOR.....	MARSHALL, ROBERT P
NIDR PROJECT OFFICER.....	KAKEHASHI, SAMUEL
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

DEVELOPMENT OF ARTIFICIAL DENTAL ANCHORS

OBJECTIVES AND WORK SCOPE:

The contractor will study at least four materials as dental implants. This will include Titanium, void metal composite; Titanium, powder metallurgy product; Alumina porcelain; and Magnesium aluminate spinel. These materials will be characterized by physical tests and implants designed to optimize desirable characteristics will be implanted in swine jaws and subjected to clinical and microscopic examinations to determine their clinical efficacy. A special scanning electron microscope examination of frozen-fractured specimens of the bone material interface will be performed.

SALIENT RESULTS TO DATE:

Our study on the effect of constant, high sucrose diet on the streptococci composition of plaque shows that the percent of S. mutans increased over a 4 week period and that the percent of S. sanguis increased initially and then declined during a 4 week period. Further study of the clinical effects of the inclusion of sodium trimetaphosphate (TMP) in a high sucrose diet (200 g/day) showed that diets containing TMP produced apparent increases in mean values of lactobacilli, veillonella and neisseria per mg of plaque. High sucrose diets supplemented with TMP also produced an apparent decline in dextranase producing organisms per mg of plaque and increased the values of specific glucosetransferase and fructosyltransferase activities. Addition of TMP to typticase-soy agar plates appeared to decrease the colony size of S. sanguis 10558 but had no apparent effect on the colony sizes of S. mitis JC43, S. mutans BHT or MZ61.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22003-05
ORGANIZATION.....	WORLD HEALTH ORGANIZATION
ADDRESS.....	1211 GENEVA 27
INITIAL START DATE.....	10-01-71
EXPIRATION DATE.....	10-31-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	BARMES, DAVID E
NIDR PROJECT OFFICER.....	SENNING, RICKLEY S
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

ETIOLOGY OF DENTAL CARIES IN PAPUA-NEW GUINEA

OBJECTIVES AND WORK SCOPE:

The Contractor will perform: A thorough and complete comparative evaluation in young human subjects of the test slab lesions as contrasted to natural lesions, utilizing all available procedures for measurement; A thorough and complete comparative evaluation in young human subjects of the microbial and biochemical compositions of test slab versus natural plaque; After the intraoral cariogenicity system has been sufficiently validated in the opinion of the Project Officer, a series of test variables may be imposed upon the model system to determine their relation to the promotion or inhibition of caries development.

SALIENT RESULTS TO DATE:

Collection of food and soil samples was completed and subcontracts for analysis of these samples were let. Identification and quantification of streptococci and associated microorganisms from UL-2 plaque was completed in addition to determinations of Ca, Mg, and K in saliva. Analysis for all elements in enamel was completed. A subcontract was let to investigate genetic diversity within and between villages with various levels of caries activity. A system for statistical analysis was developed and tested on preliminary data. This system allows for the addition of new variables and their assessment on an ongoing basis. Analysis for various carbohydrates begun under subcontract. Progess was in accordance with the workscope and satisfactory.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22005-04
ORGANIZATION.....	ROYAL DENTAL COLLEGE
ADDRESS.....	AARHUS, DENMARK
INITIAL START DATE.....	09-01-71
EXPIRATION DATE.....	09-30-73
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	SCHIOTT, D RINDOM
NIDR PROJECT OFFICER.....	CARLOS, JAMES P
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

LONGITUDINAL STUDY OF CHLORHEXIDINE

OBJECTIVES AND WORK SCOPE:

The Contractor shall conduct a controlled clinical study to: Test the long term effect of chlorhexidine on the development of dental plaque, caries, and periodontal changes; Examine the microflora of the saliva, gingiva, and tooth surfaces during such treatment; and Assess possible systemic and local side effects of long term use of chlorhexidine. The following was added to the existing Scope of Work: Gingival biopsy samples will be obtained from study subjects and examined microchemically and microscopically to determine any effect of chlorhexidine on gingival metabolism, architecture, and keratin-producing mechanisms.

SALIENT RESULTS TO DATE:

Results of clinical findings on Caries and Gingivitis after one year are being processed. Microbiological analyses have demonstrated reduction of total salivary microflora, no overgrowth of gram negative rods, and a slight reduction in relative proportion of S. Mutans in the Chlorhexidine treated group. No undesirable side reactions, except the expected mild tooth staining, have been observed.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22030-05
ORGANIZATION.....	UNIVERSITY OF ALABAMA
ADDRESS.....	BIRMINGHAM AL
INITIAL START DATE.....	11-15-71
EXPIRATION DATE.....	10-14-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	KOULOURIDES, T
NIDR PROJECT OFFICER.....	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

EVALUATE INTRAORAL TEST OF HUMAN CARIOGENICITY

OBJECTIVES AND WORK SCOPE:

The Contractor will perform: A thorough and complete comparative evaluation in young human subjects of the test slab lesions as contrasted to natural lesions, utilizing all available procedures for measurement; A thorough and complete comparative evaluation in young human subjects of the microbial and biochemical compositions of test slab versus natural plaque; After the intraoral cariogenicity system has been sufficiently validated in the opinion of the Project Officer, a series of test variables may be imposed upon the model system to determine their relation to the promotion or inhibition of caries development.

SALIENT RESULTS TO DATE:

Seven sugars and sugar alcohols were compared to sucrose for cariogenicity when used as extraoral supplements to diets containing customary levels of sucrose. Regardless of the use of gauze overlays on the enamel surface, results corresponded well with those from rat feeding experiments at U.A.B. Fluoride at 10PPM was more effective than at IPPM. Sodium glycerophosphate and TMP at 1% concentration added to 3% sucrose supplements abolished the cariogenicity of the sugar. If the enamel is softened by mild acid etch or by exposure to oral environment, the beneficial effect to fluoride was found increased. Fluoride biopsies showed selective deposition of fluoride in the 2-4 micron superficial layers of pre-softened enamel. Streptococcus sanguis appeared to be the primary colonizer for ICT and natural plaque formation. This same bacterial species appeared to be the primary colonizer at interproximal sites of both caries-free and caries-active children. Str. mutans was absent or in low numbers in ICT and natural plaques of both caries-free and caries-active subjects. Progress has been good but tends to be diffuse through examination of two many variables.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22039-03
ORGANIZATION.....	EASTMAN DENTAL CENTER
ADDRESS.....	ROCHESTER NY
INITIAL START DATE.....	10-26-71
EXPIRATION DATE.....	01-25-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	BIBBY, BASIL G
NIDR PROJECT OFFICER.....	ROGERS, WILLIAM E
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

EVALUATION OF CARIOCENICITY OF SNACK FOODS

OBJECTIVES AND WORK SCOPE:

Independently and not as an agent of the Government, the Contractor shall exert its best efforts to define which foodstuffs are more harmful or less harmful to the teeth in regard to caries. Tests shall be carried out in rats to determine the effect of using the less harmful ones. In addition, the Contractor intends to delineate snack materials to replace those of high cariogenicity. Specifically, the Contractor shall perform, but not necessarily be limited to, the following efforts: Test various human snack foods and confections for their effects on enamel dissolution, food retention, and plaque pH; and Test human foods considered to be most and least cariogenic utilizing rats.

SALIENT RESULTS TO DATE:

Performance of work has been directed mainly toward laboratory-type studies. Various foodstuffs were tested for their influence on enamel dissolution, food retention, and plaque pH. An "artificial mouth" was developed and brought to a working level. This interesting, unique new system permits quick, easy evaluation of the effects of various foods on enamel dissolution. The Contractor has not yet assembled and analyzed sufficient data to delineate what foods are more or less cariogenic (based on laboratory testing). But this is imminent and will, no doubt, be accomplished before the periodic rat feeder arrives, is assembled, and brought to a working level.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22045-01
ORGANIZATION.....	AMERICAN DENTAL ASSOCIATION
ADDRESS.....	CHICAGO IL
INITIAL START DATE.....	11-01-71
EXPIRATION DATE.....	10-31-73
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	HEFFERREN, JOHN J
NIDR PROJECT OFFICER.....	KAKEHASHI, SAMUEL
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

DETECTION OF DENTAL CARIES IN CYSTIC FIBROSIS PATIENTS

OBJECTIVES AND WORK SCOPE:

In the studies and investigations relative to early detection and characterization of dental caries in cystic fibrosis patients, the Contractor's effort during this twelve-month period of renewal shall be limited to continuing the study of the initial test and control populations to provide evidence that "altered areas" progress into clinical caries.

SALIENT RESULTS TO DATE:

The Contractor spent approximately 1/3 to 1/2 time of the first contract year acquiring and calibrating the necessary instrumentation In the remaining contract time, he has accumulated a modest base of data comparing caries detection by way of a normal clinical (visual-tactual) examination, radiographic examination, and ultraviolet light examination Tabulated results show twice as many "altered areas" of tooth surface detected by ultraviolet examination as by clinical examination. The ultraviolet fluorescent data was obtained using color film and the human eye as detectors.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22400-02
ORGANIZATION.....	UNIVERSITY OF MIAMI
ADDRESS.....	CORAL GABLES FL
INITIAL START DATE.....	01-01-72
EXPIRATION DATE.....	12-31-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	ZINNER, DORAN D
NIDR PROJECT OFFICER.....	SHERN, ROALD J
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

FLUORIDE UPTAKE IN TOOTH ENAMEL

OBJECTIVES AND WORK SCOPE:

Contractor shall provide all necessary staff, facilities, and populations to carry on a field trial of a topical fluoride study to: Assess the level of enamel fluoride attained after a series of treatments of topical gel to teeth of children consuming fluoride deficient water; Assess the rate of loss of fluoride from enamel after treatments have been completed; and Assess the residual anti-caries effect of three short treatment regimens.

SALIENT RESULTS TO DATE:

The examinations of 650 students and the biopsy of 170 student subsample was conducted in February, 1973, as contracted. The data shows no definitive results for either response. However, a mean reduction in caries in the drug-treated groups suggests that a second year will demonstrate some drug efficacy.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22401-01
ORGANIZATION.....	PENNSYLVANIA STATE UNIVERSITY
ADDRESS.....	UNIVERSITY PARK PA
INITIAL START DATE.....	02-27-72
EXPIRATION DATE.....	02-26-74
ORGANIZATION CODE.....	INT
PROJECT DIRECTOR.....	MUNGER, BRYCE L
NIDR PROJECT OFFICER.....	BOSMA, JAMES F
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

STUDY OF DEVELOPMENT OF ORAL SENSORY RECEPTORS

OBJECTIVES AND WORK SCOPE:

The contractor will continue the breeding of animals, the terminal and histological preparations, and the microscopic and ultramicroscopic studies of the sensory innervation of the oral mucosa. He will also attempt to extend these studies to stillborn human fetuses as these become available in the Hershey Medical Center. In addition, he will undertake neurophysiological studies of oral mucosal sensory receptor correlated with histological studies. Attention initially will be directed toward mechanoreceptors, using an elegant electromechanical stimulating system. Employing a currently available computer resource, the sensory signal will be traced neurophysiologically in single fivers of the nerve, in the peripheral ganglia, and in the primary nuclei of these bulbar nerves.

SALIENT RESULTS TO DATE:

To date 10 rhesus have been sacrificed and a very large number of sections have been completed and studied by light or electron microscopy. From this study, the general patterns of sensory receptors in the tongue, lip and palate have been described, along with the general sequence of their formation. Dr. Munger has described and demonstrated two remarkable findings: discrete rows of concentrations of sensory receptors in the margin of the tongue and also in the corrugations of the bony palate. Dr. B. Pubols of the Hershey Dept. of Anatomy, and Dr. R. Dubner of NIDR have been engaged in physiological studies in correlation with detailed histology at site. Histological studies have been performed on the skin and mucocutaneous junction of the nasal area, in comparison with the lip. Also of the mucosa of the epiglottis, in comparison with the hard palate, and of the mucosa of the soft palate and pharynx wall, in comparison with tongue. So far histological studies have been initiated on 3 human abortuses and one premature infant. There are several other abortuses in prospect, from clinically necessary pregnancy interruptions.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22402-02
ORGANIZATION.....	DUKE UNIVERSITY
ADDRESS.....	DURHAM NC
INITIAL START DATE.....	05-17-72
EXPIRATION DATE.....	05-16-75
ORGANIZATION CODE.....	INT
PROJECT DIRECTOR.....	DANIELS, CHARLES A
NIDR PROJECT OFFICER.....	NOTKINS, ABNER L
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

RHEUMATOID FACTOR AND INFECTIOUS ANTIBODY COMPLEXES

OBJECTIVES AND WORK SCOPE:

The contractor proposes to test the ability of different concentrations of rheumatoid factor, complement, rheumatoid factor plus complement, Ctg and cryoglobulins to neutralize infectious virus-antibody complexes. Herpes simplex, vaccinia influenza and hepatitus virus will serve as models. Fixation of complement by the alternate pathway and lysis of sensitized virus by complement also will be studied.

SALIENT RESULTS TO DATE:

During the first year of the contract, it was shown that earlier studies with herpetic simplex virus and rheumatoid factor could be repeated with vaccinia virus indicating the general nature of this phenomena. It was also shown that neutralization of herpes simplex virus and the destrection of herpes simplex virus-infected cells by antiviral antibody and complement could be accomplished far more effectively by the classic rather than alternate complement pathway. Last year he showed that rheumatoid factor was present in over 50% of the sera obtained from patients with hepatitis B virus antigenemia and that rheumatoid factor could interact with hepatitis B antigen-antibody complexes. Other experiments showed that rheumatoid factor could attach to virus-infected cells and would inhibit the complement mediated lysis of these cells. Dr. Daniels now plans to extend these in vitro observations to in vivo systems in animals and man. The plans for the next 12 months are a clear-cut and logical extension of the observations made over the last two years.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22403-02
ORGANIZATION.....	UNIVERSITY OF ALABAMA
ADDRESS.....	BIRMINGHAM AL
INITIAL START DATE.....	06-05-72
EXPIRATION DATE.....	12-04-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	NAVIA, JUAN M
NIDR PROJECT OFFICER.....	ROGERS, WILLIAM E
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

DEVELOPMENT SUGAR-SUBSTITUTED FOODS LOW CARIES POTENTIAL

OBJECTIVES AND WORK SCOPE:

The Contractor shall formulate, manufacture, and test in the laboratory a group of snack foods which have been modified by substitution of the sucrose with other carbohydrates to reduce its caries promoting properties. Specifically, the Contractor shall: Evaluate by conventional rat caries tests the relative cariogenicity of various sweetening agents when substituted for various levels of sucrose in the diet; Design and develop taste-acceptable (to humans) snack foods and desserts which would contain sucrose substituted sweetening agents of low cariogenicity to the rat; and Test for cariogenicity (in rats) snack foods in which low cariogenic sweetening agents have been used.

SALIENT RESULTS TO DATE:

Development of the rat assay: The second Konig Feeder has just been received. Food consumption and body weight gain data has been obtained using the old feeder. Evaluation of the caries potential of several carbohydrates: Fourteen carbohydrates have been tested for caries promotion in four large ad lib feeding experiments. These experiments show Buccal Scores ranging from 6 (pectin) to 15 (sucrose) and 18 (B lactose). Interestingly, fructose was 15, glucose 13, and dextran 11. A series that was generally similar was obtained for Sulcal Scores. Cariogenic properties largely parallel the sweetness of the carbohydrates. Some results show that combinations of carbohydrates have lower caries-promoting capacity than the individual sugars at lower concentration. Formulation of acceptable snack foods: Caramel candy, sugar cookies, and oatmeal cookies have been developed that pass a flavor test and that have reduced levels of sucrose, typically 15% of customary. Development of successful formulas appear to have been achieved with difficulty. Low sucrose puddings also have been prepared. The caries-promoting activity of certain of these snacks now is being assayed. Objectives of workscope are closely followed.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22404-02
ORGANIZATION.....	UNIVERSITY OF FLORIDA
ADDRESS.....	GAINESVILLE FL
INITIAL START DATE.....	05-16-72
EXPIRATION DATE.....	07-31-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	OLSON, GERALD A
NIDR PROJECT OFFICER.....	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

STUDY OF CARIES-INHIBITORY ACTIVITY IN HUMAN SALIVA

OBJECTIVES AND WORK SCOPE:

The Contractor shall investigate the existence and delineate the prevalence of naturally occurring caries inhibitory factors in human saliva. Specifically, he shall perform the following: Saliva shall be collected from at least 100 subjects; Information relative to caries experience shall be recorded for each human subject which shall include oral examinations for DMFT, and other pertinent data as required for clinical evaluation of present and past caries activity; All saliva samples shall be subjected to quantitative in vitro assay for adherence inhibitory activity of saliva as tested against at least six strains of Streptococcus mutans.

SALIENT RESULTS TO DATE:

Over sixty human saliva samples have been assayed for their adherence inhibitory activity (AID). An apparent trend exists between higher AIA and lower DMFT scores. However, the converse relationship lacks validity. Statistical analyses comparing fewer variables may serve to clarify this somewhat muddied picture. Some characteristics of the salivary factor are; non-dialyzability; heat stability at 56 degrees C; and selective inhibition of certain mutans strains. Further characterization of the factor will be done. Extensions of the use of several mutans strains in the AIA has uncovered new cross-relationships. Shared antigens between some mutans strains have been recognized by the use of S. mutans antisera in the AIA. Inhibition of dextran-sucrose-induced agglutination appears to correlate with AIA relationships. However, antibody to glucosyltransferase indicates immunologic identity in the AIA but diversity in the agglutination-inhibition test. Further work on these relationships should increase our knowledge of strain diversity and the role of transferases within the mutans group.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22406-01
ORGANIZATION.....	RESEARCH FOUNDATION OF STATE UNIVERSITY OF NY
ADDRESS.....	ALBANY NY
INITIAL START DATE.....	06-12-72
EXPIRATION DATE.....	08-31-75
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	ENGLISH, JAMES A
NIDR PROJECT OFFICER.....	JOLY, OLGA
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

DEGREE OF EFFECTIVENESS OF CARIES PREVENTIVE PROCEDURES

OBJECTIVES AND WORK SCOPE:

Effectiveness of a combined series of caries-preventive measures will be evaluated in 1500 students (6-7-8th grades) in Buffalo, New York. All will undergo standard preventive measures: fluoridated drinking water, restorative dental care, oral hygiene instruction, and prophylactic treatment. Additionally, Test Groups will get adhesive sealant applied to pit and fissure tooth areas followed by topical application of acidulated fluoride phosphate solution. One Test Group will also be given special oral hygiene instruction and unusual encouragement to seek appropriate dental care; selected individuals, moreover, will receive specific behavioral procedures designed to emphasize motivational incentives to change oral hygiene behavior.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22407-02
ORGANIZATION.....	UNIVERSITY OF MINNESOTA
ADDRESS.....	MINNEAPOLIS MN
INITIAL START DATE.....	05-02-72
EXPIRATION DATE.....	11-01-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	LILJEMARK, WILLIAM F
NIDR PROJECT OFFICER.....	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

AGENTS AFFECTING ADHERENCE OF CARIOGENIC MICROORGANISMS

OBJECTIVES AND WORK SCOPE:

The Contractor shall perform the following efforts: (1) Isolate and characterize the "fuzzy coats" of Streptococcus salivarius, Streptococcus sanguis, Streptococcus miteor, and Streptoccocus mutans. (2) Use appropriate radioisotopic tags to isolate and characterize the soluble and insoluble dextrans from the same organisms. (3) Utilize the "fuzzy coats", radiolabeled dextrans, and radiolabeled bacteria to analyze the site-specific interactions which result in the selective adherence of oral streptococci to enamel powder and hydroxyapatite. (4) Analyze the effectiveness of a variety of agents including polysacchaharases, proteases, lipases, low molecular weight dextrans, and detergents which might inhibit the development of sucrose-caused plaque by blocking specific sites of the components involved in adherence.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22409-02
ORGANIZATION.....	HUNTINGTON RESEARCH CENTER
ADDRESS.....	BALTIMORE MD
INITIAL START DATE.....	06-12-72
EXPIRATION DATE.....	03-31-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	WILSNACK, ROGER E
NIDR PROJECT OFFICER.....	HAGEAGE, GEORGE J
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

ANTIBODY IDENTIFICATION OF CARIOGENIC S. MUTANS

OBJECTIVES AND WORK SCOPE:

The research plan for the extension would be to prepare, characterize, and test specific conjugates generated during the final two months of the original project. These conjugates would be derived from antisera produced in rabbits against the five serogroups of S. mutans using as an immunogen li[illegible]d formalin-killed cells as well as cell wall antigens.

SALIENT RESULTS TO DATE:

Huntingdon has made satisfactory progress in the performance of the contract. By the end of the first eight months they had: amassed thirty strains of S. mutans for use as immunogens, for evaluating staining efficiency of the antisera, and for use in adsorption studies; screened goats, rabbits, and pigs for the presence of natural antibody to the five serogroups of S. mutans as well as to other oral bacteria; immunized the three animal species with whole cell antigens (heat-killed versus formalinized versus live cells) and cell wall antigens of representatives of the five serogroups of S. mutans; evaluated goat and rabbit antisera prepared against heat-killed immunogens as to their specificity; and initiated fractionation and conjugation of this antisera. It is anticipated that by the end of the contractual period Huntingdon will have prepared, characterized, and evaluated FITC conjugates prepared from this antisera (d) and will have produced and tested for specificity antisera against S mutans generated from live and formalin-killed whole cells and cell walls.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22410-02
ORGANIZATION.....	UNIVERSITY OF MICHIGAN
ADDRESS.....	ANN ARBOR MI
INITIAL START DATE.....	06-30-72
EXPIRATION DATE.....	06-30-76
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	BAGRAMIAM, ROBERT A
NIDR PROJECT OFFICER.....	DRISCOLL, WILLIAM S
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

A COMBINED SERIES OF CARIES PREVENTIVE PROCEDURES

OBJECTIVES AND WORK SCOPE:

The Contractor shall complete a three year study to determine the degree of effectiveness of a combination of several caries-preventive measures in a population of children in a Michigan community. A total of 1200 students shall be selected from elementary schools in the optimally fluoridated city of Ypsilanti by utilizing 600 each from Grades 1 and 6. At various intervals of time the children will receive prophylaxis, application of adhesive sealants, application of phosphate-fluoride gel, oral hygiene education and technique instruction, and restorative dental care. Interim technical reports, summaries, and a final report is required.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22412-02
ORGANIZATION.....	CANCER RESEARCH CENTER
ADDRESS.....	COLUMBIA MO
INITIAL START DATE.....	06-30-72
EXPIRATION DATE.....	06-29-75
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	GUERRA, OSCAR N
NIDR PROJECT OFFICER.....	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

ANALYSIS ORAL FLUIDS IN HIGH-INCIDENCE CARIES POPULATION

OBJECTIVES AND WORK SCOPE:

Study the causal factors of dental caries by evaluating the interaction and interrelationship between oral flora and the biochemical changes undergone by oral fluid during radiation therapy. Specifically, the Contractor shall select approximately 30 subjects each year who are receiving at least 4,000 rads of radiation treatment for head and neck cancer, and who will receive initially no antibiotic or fluoride therapy. Scrapings from teeth of the subjects shall be used for biochemical analysis to be obtained prior to treatment, during therapy, and after discharge from the Hospital.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22413-02
ORGANIZATION.....	UNIVERSITY OF PENNSYLVANIA
ADDRESS.....	PHILADELPHIA PA
INITIAL START DATE.....	06-29-72
EXPIRATION DATE.....	12-28-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	CAGAN, ROBERT H
NIDR PROJECT OFFICER.....	ROUSSOS, GERASSIMOS
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

EVALUATION OF THE SWEET-TASTING PROTEIN MONELLIN

OBJECTIVES AND WORK SCOPE:

Conduct studies to biochemically characterize a sweet-tasting protein (Monellin) which has been isolated from the berries of a tropical plant, Dioscoreophyllum cumminsii, as possible application as a substitute for sucrose, particularly in snack-type foods. Contractor shall isolate the protein, determine the molecular weight and isoelectric point, ascertain the UV and fluorescent spectra, determine the amino acid composition including cysteine, cystine, tryptophan, and amide moiety, and perform appropriate degradation studies.

SALIENT RESULTS TO DATE:

Monellin, an intensely sweet substance from the fruit of the tropical plant Dioscoreophyllum cuminsii, has been clearly established to be a protein. The molecular weight of monellin was estimated by two independent physical methods. The values were 10,000 and 10,500 and agreed with minimal molecular weights based on chemical analyses. The molecular weight calculated from amino acid analysis is 10,700, and the protein consists of a single polypeptide chain of approximately 91 amino acids. The protein contains no histidine, and only one residue each of tryptophan, cysteine, and methoionine are present. It contains no monoor dimethyl derivatives of lysine or arginine. Fifteen basic residues (Lys + Arg) and 22 acidic residues (Asp + Glu) are present, but up to six of the latter may be in the amide form. Isoelectric focusing established the isoelectric point of monellin to be 9.3. Further studies have been conducted to attempt to degrade monellin into smaller fragments. These preliminary studies have used either chemical or enzymatic means in an attempt to produce a sweet-tasting fragment.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22414-03
ORGANIZATION.....	LITTON BIONETICS, INC
ADDRESS.....	BETHESDA MD
INITIAL START DATE.....	06-30-72
EXPIRATION DATE.....	06-29-75
ORGANIZATION CODE.....	INT
PROJECT DIRECTOR.....	MACKLER, BRUCE F
NIDR PROJECT OFFICER.....	MERGENHAGEN, STEPHAN
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

ISOLATION & CHARACTERIZATION ANTIGENS FROM HUMAN PLAQUE

OBJECTIVES AND WORK SCOPE:

Independently, and not as an agent of the Government, the Contractor shall exert its best efforts to conduct studies, as necessary, to isolate and identify antigens in human dental plaque which have the potential to transform lymphocytes from patients with periodontal disease and to characterize biologically-active effector molecules such as lymphotoxin and bone resorbing factors, produced in tissue culture cell lines or by lymphocytes when stimulated by plaquederived or other antigens or mitogens.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE22415-01
ORGANIZATION.....	UNIVERSITY OF MINNESOTA
ADDRESS.....	MINNEAPOLIS MN
INITIAL START DATE.....	06-29-72
EXPIRATION DATE.....	01-31-76
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	LILJEMARK, WILLIAM F
NIDR PROJECT OFFICER.....	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

STREP & POLYSACCHARIDE FORMING ABILITY OF DENTAL PLAQUE

OBJECTIVES AND WORK SCOPE:

The major purpose of this research is to evaluate specific microorganisms and sucrose activity of plaque samples as an indicator of future caries potential.

SALIENT RESULTS TO DATE:

The study is progressing as outlined in the original contract proposal. The polysaccharid forming ability of dental plaque as quantitated by our method was not significantly associated with caries prevalence. The relative percentages of S. mutans and lactobacilli were the only microorganisms to show significant positive association with caries prevalence. Together they explained nearly eight per cent of the variance in total caries prevalence. The second plaque sampling has been concluded with a loss of 14.5% of the subjects. This attrition was primarily due to changes in school boundaries. In addition to differentiating and quantitating the cariogenic microorganisms by colonial morphology a selective media for S. mutans and the quantitation of total plaque by turbidity has been added to the study protocol. The third plaque sampling will begin in March 1974. This phase in the study will provide information regarding one year incidence of caries. A summary of these findings as well as changes in oral micoorganisms at six month intervals will be available in the January, 1975 progress report and summary.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE32405-01
ORGANIZATION..	CENTRAL INSTITUTE FOR EXPERIMENTAL ANIMALS
ADDRESS.....	TOKYO, JAPAN
INITIAL START DATE.....	09-14-72
EXPIRATION DATE.....	09-13-74
ORGANIZATION CODE.....	EXP
PROJECT DIRECTOR.....	NISHIMURA, HIDEO
NIDR PROJECT OFFICER.....	CHRISTIANSEN, R L
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

PRENATAL DEVELOPMENT OF HUMAN ORAL AND FACIAL STRUCTURES

OBJECTIVES AND WORK SCOPE:

A Manuscript entitled "Prenatal Development of the Human with Specific Reference to Oral-Facial Structures" is aimed at publication of a monograph under the authorship of Dr. Hideo Nishimura on complete descriptive study of the normal and abnormal development of human embryo and fetus with special reference to the head and oral-facial complex. This will furnish dentists, oral surgeons, and other biomedical scientists with the most reliable standard for their studies on the related subjects. The manuscript will be for disposition by the National Institute of Dental Research.

SALIENT RESULTS TO DATE:

The Principal Investigator and his group collected 1,335 human embryonic and 202 fetal specimens and those were added to his collection obtained so far. By using a number of normal embryonic and fetal specimans (stage: 2mm = 35cm in CR length) selected from the collection, various developmental features of the oral-facial and related structures were photographed. Items of the prepared serial pictures and their numbers are as follows: lateral view of the whole body, 20; front view of the face, 20; oblique view of the face, 12; view of the branchial arches, 9; view of the optic region, 4; view of the lip, 5; view of the gum, 3; and view of the roof of the oral cavity, 7. Among the above pictures, those at the early embryonic stage are especially valuable in terms of that those have never been prepared elsewhere.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE32408-01
ORGANIZATION.....	ROYAL COLLEGE OF SURGEONS OF ENGLAND
ADDRESS.....	LONDON, ENGLAND
INITIAL START DATE.....	12-04-72
EXPIRATION DATE.....	12-03-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	COLE, MICHAEL F
NIDR PROJECT OFFICER.....	LARSON, RACHEL H
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

STUDY OF EFFECT OF DIETARY ADDITIVES ON PLAQUES & CARIES

OBJECTIVES AND WORK SCOPE:

Plaque chemistry and caries incidence will be determined in 12-16 month old monkeys maintained on a cariogenic diet, with and without supplements of potential anti-cariogenic substances: pyridoxine and sodium inositol phosphate. Plaque samples obtained before and during the feeding experiments will be examined for numbers of microorganisms producing extracellular and intracellular polysaccharides, and also for the quantities of calcium phosphorus, magnesium, carbohydrate, and protein. The identity of the acids produced in situ by plaque from sugars in the different diets will be determined.

SALIENT RESULTS TO DATE:

Progress on this contract during the past year has been in keeping with the proposed schedule. A larger group of monkeys has been brought in from the wild, subjected to testing and treatment after which 24 of the most desirable were selected and set up in the three experimental groups. The necessary equipment for assays has been purchased or assembled, including installation and calibration when needed. Test procedures have been selected, modified where necessary, and reliability established. Both baseline and early experimental data have been collected and the whole study appears to the project officer to be off to an excellent start.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE32416-00
ORGANIZATION.....	GENERAL MILLS, INC
ADDRESS.....	MINNEAPOLIS MN
INITIAL START DATE.....	11-15-72
EXPIRATION DATE.....	11-14-73
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	ANDERSON, RAY H
NIDR PROJECT OFFICER.....	ROGERS, WILLIAM E
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

STUDY OF SUCROSE SUBSTITUTES

OBJECTIVES AND WORK SCOPE:

The Contractor shall exert its best efforts to conduct feasibility studies and investigations to achieve the following objective: Formulate, manufacture, and taste-test a variety of foods normally containing high contents of sucrose but which have been modified by substitution of the sucrose with other carbohydrates to reduce their caries-producing potential. The re-formulated products shall have the lowest level of sucrose feasible consistent with retention of properties that would still render the new products acceptable for human consumption. Analyze, interpret, and report the data resulting from performance of this effort.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE32417-01
ORGANIZATION.....	LITTON BIONETICS, INC
ADDRESS.....	BETHESDA MD
INITIAL START DATE.....	04-22-73
EXPIRATION DATE.....	06-30-74
ORGANIZATION CODE.....	INT
PROJECT DIRECTOR.....	KINGSBURY, ELIZABETH
NIDR PROJECT OFFICER.....	GIBSON, WILLIAM A
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

EM HYDROLYTIC ENZYMES IN PERIO LIGAMENT OF RAT

OBJECTIVES AND WORK SCOPE:

The Contractor shall conduct studies and investigations, as necessary, to provide suitable tissue preparation and staining techniques for the ultrastructural localization of the following enzyme activities in mineralized tissues of the rat jaw: Aryl sulfatase, 5'-Nucleotidase, Thiamine pyrophosphatase, and N-acetylglucosaminidase. Techniques shall also be presented for validating enzyme localization and identification of the associated cell types. The ultrastructural localization of such enzyme activities shall be consistent with the reported light microscope findings.

SALIENT RESULTS TO DATE:

The electron microscopic aspects of the localization of thiamine pyrophosphatase (TPPase) is essentially complete. It is present in osteoclasts and fibroblasts, but none or very little is present in osteocytes. The ultrastructural localization of aryl sulfatase (ASase) has been achieved with a staining technique which differs from that used by Gibson and Fullmer. This has been necessary because the latter technique is unsuitable for the electron microscope. Thus there is a problem in determining whether the perivascular cells which show the stain are identical to those described by Gibson and Fullmer.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE32418-01
ORGANIZATION.....	NEW YORK MEDICAL COLLEGE
ADDRESS.....	NEW YORK NY
INITIAL START DATE.....	04-16-73
EXPIRATION DATE.....	05-31-76
ORGANIZATION CODE.....	INT
PROJECT DIRECTOR.....	PULLMAN, IRA
NIDR PROJECT OFFICER.....	FOWLER, BRUCE O
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

APATITIC CRYSTALS AND MINERAL-PROTEIN COMPLEXES

OBJECTIVES AND WORK SCOPE:

The contractor shall conduct electron paramagnetic resonance studies of apatite structure and mineral-matrix bonding to include a series of synthetic as well as biological apatite samples and specimens. These shall be irradiated and examined in order to characterize the free radical species produced and to interpret same in terms of their molecular structural environments. Such studies are also to include a series of calcium phosphate macromolecule complexes which are to be examined by spin probe and spin transfer procedures. The purpose of these experiments is to establish chemical bonding sites between molecule and macromolecule in each complex. The results of same will be reported as the work progresses.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE32419-01
ORGANIZATION.....	AMERICAN DENTAL ASSOCIATION
ADDRESS.....	CHICAGO IL
INITIAL START DATE.....	04-30-73
EXPIRATION DATE.....	04-10-74
ORGANIZATION CODE.....	INT
PROJECT DIRECTOR.....	STEFFEK, ANTHONY J
NIDR PROJECT OFFICER.....	JOHNSTON, MALCOLM C
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

ELECTRON MICROSCOPY OF MIGRATING EMBRYONIC CELLS

OBJECTIVES AND WORK SCOPE:

The technique of steroscan electron microsopy has been utilized by our division in an attempt to complement current techniques in describing facial formation and has greatly facilitated the assessment of facial development both at the early and later stages of development. The objectives of the present proposal are to extend our initial experiments in characterizing the early morphogenesis of neural crest migration with steroscan electron microscopy.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE32420-01
ORGANIZATION.....	CLEMSON UNIVERSITY
ADDRESS.....	CLEMSON SC
INITIAL START DATE.....	05-01-73
EXPIRATION DATE.....	05-01-76
ORGANIZATION CODE.....	EXP
PROJECT DIRECTOR.....	KLAWITTER, JEROME J
NIDR PROJECT OFFICER.....	KAKEHASHI, SAMUEL
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

HISTOLOGICAL ACCEPTANCE OF ARTIFICALLY FABRICATED TEETH

OBJECTIVES AND WORK SCOPE:

Incisor shaped teeth fabricated from a crome cobalt alloy, poly-methylmethacrylate, and ceramic materials will be implanted into the jaws of dogs to determine the histological acceptance of artificially fabricated teeth of different material composition in animals. Samples of the materials will be submitted to routine toxicology assay and to characterization studies. Artificial teeth will be stabilized for a period of two months. Clinical evaluation and radiographic evaluation of the artificial teeth will be performed after implant time periods ranging from one month. Tissue blocks containing implanted teeth will be removed periodically to assess response at the microscopic level. Sufficient teeth will be implanted to permit statistically valid conclusions as to the histological acceptance of each material.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE32421-01
ORGANIZATION.....	UNIVERSITY OF FLORIDA
ADDRESS.....	GAINESVILLE GA
INITIAL START DATE.....	05-07-73
EXPIRATION DATE.....	05-01-76
ORGANIZATION CODE.....	EXP
PROJECT DIRECTOR.....	STANLEY, HAROLD R
NIDR PROJECT OFFICER.....	KAKEHASHI, SAMUEL
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

HISTOLOGICAL ACCEPTANCE OF ARTIFICALLY FABRICATED TEETH

OBJECTIVES AND WORK SCOPE:

Conduct a study to determine the histological acceptance of artificially fabricated teeth made from the following materials: poly-methylmethacrylate, a crome cobalt alloy, and a ceramic or bioglass-ceramic. Artificial incisor teeth will contain a porous coating of the same material used in preparing the solid portion of the root and will be implanted in baboons. Samples of the materials will be submitted to routine toxicology assay and to characterization studies. Artificial teeth will be implanted into the natural socket in baboons and will be stabilized for a period of three months. Clinical and radiographic evaluation of the artificial teeth will be performed after implants have been in place for more than one month. Tissue blocks will be removed to assess response at microscopic level. Sufficient teeth will be implanted to permit statistically valid conclusions as to the histological acceptance of each material.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE32422-01
ORGANIZATION.....	HARVARD UNIVERSITY
ADDRESS.....	CAMBRIDGE MA
INITIAL START DATE.....	05-18-73
EXPIRATION DATE.....	05-17-76
ORGANIZATION CODE.....	EXP
PROJECT DIRECTOR.....	SHULMAN, LEONARD B
NIDR PROJECT OFFICER.....	KAKEHASHI, SAMUEL
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

A STUDY OF ARTIFICIAL TEETH

OBJECTIVES AND WORK SCOPE:

The Contractor shall exert his best efforts to determine the histologic acceptance of teeth artificially fabricated from the polymer of reagent grade methylmethacrylate, formed in a variety of "root" designs and implanted into the jaws of baboons. Specifically, the Contractor shall: Select representative incisor shaped teeth fabricated in the following root forms: natural tooth replica, preformed natural tooth, and blades; Determine the effect on acceptability of smooth versus porous root surfaces and also the effects of preparing the root surface with slots and grooves; Perform clinical evaluation and radiographic evaluation of the artificial teeth after implant time periods ranging from one (1) week; Remove tissue blocks containing the implanted teeth periodically to assess response at the microscopic level. Sufficient teeth shall be implanted to permit statistically valid conclusions as to the biological and clinical acceptance of each design.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE32423-03
ORGANIZATION.....	AMERICAN DENTAL ASSOCIATION
ADDRESS.....	CHICAGO IL
INITIAL START DATE.....	05-22-73
EXPIRATION DATE.....	11-22-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	GROBMAN, HULDA
NIDR PROJECT OFFICER.....	FREW, RALPH A
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

STUDY OF METHODS OF DELIVERING CARIES PREVENTION

OBJECTIVES AND WORK SCOPE:

The Contractor will assess the knowledge, beliefs, attitudes, and current actions of practicing dentists relative to procedures for the prevention of dental caries. Additionally, the Contractor shall determine the potential of the preventive dentistry activities of the current delivery system for participation in a comprehensive caries prevention program for children. Finally, the Contractor shall design a study for determining the effectiveness of the dentist, singly and as a member of professional societies, in changing public attitudes and behavior relative to caries preventive measures. For the purpose of this contract, technics and agents to be considered as caries prevention shall be limited to fluoride therapy (exclusive of water fluoridation), adhesive pit and fissure sealants, personal oral hygiene education, and diet counseling.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE32424-01
ORGANIZATION.....	UNIVERSITY OF CALIFORNIA
ADDRESS.....	SAN FRANCISCO CA
INITIAL START DATE.....	06-22-73
EXPIRATION DATE.....	12-31-76
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	SILVERSTEIN, STEVEN
NIDR PROJECT OFFICER.....	MEYERS, RHEA
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

STUDY OF EFFECT OF DAILY SUPERVISED DEPLAQUING OF TEETH

OBJECTIVES AND WORK SCOPE:

From a population of 600 children between the ages of 12 and 13 years who possess a relatively high level of dental caries and gingivitis, establish one test and one control group of sufficient size to ascertain if there is a statistical difference between the test and control groups. Record dental caries for each tooth one every year. Gingival inflammation and plaque scores shall be recorded every three months. Oral hygiene procedures by the test group shall keep the tooth surface free from plaque. Wax-Flossing, brushing, and disclosing solutions shall be conducted daily by the participants under the direct supervision of the Contractor to insure the removal of visual plaque deposits. A combination of group and individual instruction along with periodic review sessions shall teach the test group the performance effective oral hygiene procedures. Analyze data.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE32425-01
ORGANIZATION.....	GULF SOUTH RESEARCH INSTITUTE
ADDRESS.....	NEW ORLEANS LA
INITIAL START DATE.....	06-29-73
EXPIRATION DATE.....	06-28-75
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	RAWLS, HENRY R
NIDR PROJECT OFFICER.....	FREW, RALPH A
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

DIAGNOSTIC SYSTEM FOR EARLY DETECTION OF DENTAL CARIES

OBJECTIVES AND WORK SCOPE:

The contractor shall exercise its best efforts in the conduct of research studies directed toward the formulation and development of a fluorescent dye penetration technique intended for the early detection of dental caries by human observers. Develop non-proprietary dye formulations which shall be evaluated in various penetrant vehicles. Conduct toxicological testing. Conduct psychophysical evaluation. Determine the convenience factors and esthetics from the results of experiments designed to test the applicability of various formulations. The results of these evaluations shall be available within ten months to permit adequate time for compilation of findings and recommendations including necessary approvals for possible in vivo study involving human volunteers. The Contractor shall submit the selected dye to the Federal Drug Administration for approval in use in clinical trials.

SALIENT RESULTS TO DATE:

Three candidate formulas for use as caries-disclosing fluids have been tested to determine their toxicological properties, their mucous-membrane irritation potential, and their ability to enhance the detectability of early-caries-like-lesions. The flourescent "active ingredients" of the three formulas were found to have no pathological effect in either rats or beagle dogs and did not have any signs of eye irritation in rabbits. Psychophysical testing of the three candidate formulas in vitro revealed statistically significant differences in lesion-disclosing performance among the formulas as compared to conventional examination methods. Progress was made in preparing IND applications for FDA, and an instrument for ultraviolet fluorescence oral examinations has been designed. The lesion-disclosing performance was limited to the detection of lesions produced by acid etching when the examiners were aware that the probability of a surface having a lesion was one in two. Performance on naturally occurring lesions was less dramatic, and reports on validity estimates with hardness as the criteria was limited to etched areas.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE32427-01
ORGANIZATION.....	STATE OF FLORIDA - DIVISION OF HEALTH
ADDRESS.....	JACKSONVILLE FL
INITIAL START DATE.....	06-29-73
EXPIRATION DATE.....	06-30-75
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	RINGELBERG, MEL
NIDR PROJECT OFFICER.....	DRISCOLL, WILLIAM S
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

TEST OF EFFICACY OF AMINE FLUORIDE MOUTHRINSE

OBJECTIVES AND WORK SCOPE:

The purpose of this study is to determine the caries-preventive effects and the effects on dental plaque and gingivitis of an amine fluoride mouthrinse and dentifrice, when used alone and when used in combination with one another. The investigation shall also compare the effects of the amine fluoride products with their respective inorganic counterparts. The starting population shall comprise 2000 children attending the sixth grades of middle schools in the nonfluoridated area of Escambia County, Florida. Each child will rinse daily with a fluoride or non-fluoride mouthwash under supervision at school, and brush daily with a fluoride or non-fluoride toothpaste without supervision at home.

SALIENT RESULTS TO DATE:

2,062 baseline examinations were completed in November. Included in the examination procedure was a visual-tactile caries surface examination, a five film bitewing radiograph examination, a modified gingival index exam and a modified Quigley-Hein plaque index exam. Two examiners divided all exams with each completing caries, gingival and plaque exams on the same individual. The data from the exam forms is now being transferred to magnetic tape for computer processing. A hand tabulation of 523 caries exams revealed a range of mean DMFS scores between groups of 3.81 to 4.60. The selection was non-random by school. Treatment regimens were begun in the eleven schools in early December. Dentifrice was mailed to all study participants and their families in December and early January. Oral hygiene instruction sessions have been given to all schools. A reinforcement of the mouthrinsing technique has been accomplished with supervising teachers and participating student. Questionaires were mailed to a 20% random sample to estimate actual dentifrice use. Plaque and gingival exams were completed on a 50% random sample twelve weeks after initiating the treatment regimens. Data from these exams is now being processed. Attrition of study participants has been minimal.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE32428-01
ORGANIZATION.....	AMERICAN DENTAL ASSOCIATION
ADDRESS.....	CHICAGO IL
INITIAL START DATE.....	08-01-73
EXPIRATION DATE.....	07-31-75
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	HEFFERREN, JOHN J
NIDR PROJECT OFFICER.....	KORTS, DAVID C
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

ETCH BIOPSY DETERMINING FLUORIDE CONTENT OF TOOTH ENAMEL

OBJECTIVES AND WORK SCOPE:

The objective of this proposal is to develop methods to systematically delineate the precision and accuracy of the sampling and subsequent steps of an abrasive and an acid etch fluoride biopsy technique for estimating fluoride content in the outermost layers of tooth enamel which are applicable to field survey requirements.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE32429-01
ORGANIZATION.....	UNIVERSITY OF IOWA
ADDRESS.....	IOWA CITY IA
INITIAL START DATE.....	08-01-73
EXPIRATION DATE.....	01-31-76
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	WEI, STEPHEN H
NIDR PROJECT OFFICER.....	KORTS, DAVID C
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

ETCH BIOPSY FOR DETERMINING FLUORIDE OF TOOTH ENAMEL

OBJECTIVES AND WORK SCOPE:

The objective of this proposal is to develop methods to systematically delineate the precision and accuracy of the sampling and subsequent steps of an abrasive and an acid etch fluoride biopsy technique for estimating fluoride content in the outermost layers of tooth enamel which are applicable to field survey requirements.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE32430-01
ORGANIZATION.....	FORSYTH DENTAL CENTER
ADDRESS.....	BOSTON MA
INITIAL START DATE.....	06-29-73
EXPIRATION DATE.....	10-31-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	LOBENE, RALPH R
NIDR PROJECT OFFICER.....	SHERN, ROALD J
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

STUDY OF ANTIMICROBIAL AGENTS

OBJECTIVES AND WORK SCOPE:

Perform a series of short-term (1-16 weeks) clinical trials of anti-microbial and anti-plaque agents, on groups of up to fifty subjects per trial. The agents to be tested will be selected, acquired, and furnished by the Government to the Contractor. The exact number of compounds to be tested is unknown; however, it is envisioned that ten study panels (up to fifty subjects each) will be required. Some study panels may be used more than once, and trials of several agents may take place simultaneously. It is expected that the populations utilized will be representative of school aged children and young adult males living in the area where the trials are conducted. Because of the small sample size to be studied, a low attrition rate is mandatory.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE42431-01
ORGANIZATION.....	INSTITUTE FOR TECHNOLOGIC INVESTIGATIONS
ADDRESS.....	BOGATA, COLOMBIA
INITIAL START DATE.....	09-18-73
EXPIRATION DATE.....	12-15-74
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	MONCADA, FELIX
NIDR PROJECT OFFICER.....	CHASSEY, BRUCE
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

EXPERIMENTAL DEVELOPMENT OF INVERT PANELA

OBJECTIVES AND WORK SCOPE:

The main objective of this research is the experimental development of invert panela for possible use in the human diet. A successful invert panela must be similar in appearance, flavor, physical consistency, and acceptance to ordinary panela. Panela, incidently, is the solid product obtained from clarifying and concentrating sugar cane juice.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE42434-01
ORGANIZATION.....	HAZELTON LABORATORIES INCORPORATED
ADDRESS.....	VIENNA VA
INITIAL START DATE.....	05-01-74
EXPIRATION DATE.....	09-30-76
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	BOYD, DALE D
NIDR PROJECT OFFICER.....	BOWEN, WILLIAM H
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

ANTI-CARIES IMMUNIZATION IN SUBHUMAN PRIMATES

OBJECTIVES AND WORK SCOPE:

The Contractor will provide 40-50 Macaca fascicularis monkeys approximately sixteen months of age. The Contractor would house and maintain the monkeys with suitable sterility and safety procedures for a period of not less than two (2) years. The monkeys would be fed eight times daily and less frequently on weekends with a special caries-conducive diet which would be specified by NIDR. The Contractor would also provide facilities for clinical (general anesthesia and minor oral surgery) and radiographic examinations.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE42435-01
ORGANIZATION.....	SOUTHERN RESEARCH INSTITUTE
ADDRESS.....	BIRMINGHAM AL
INITIAL START DATE.....	05-15-74
EXPIRATION DATE.....	05-14-75
ORGANIZATION CODE.....	EXP
PROJECT DIRECTOR.....	TANQUARY, A CHARLES
NIDR PROJECT OFFICER.....	KAKEHASHI, SAMUEL
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

IMPROVED MATERIALS FOR EXTRAORAL PROSTHESIS

OBJECTIVES AND WORK SCOPE:

Independently, and not as an agent of the Government, the Contractor shall exert his best efforts in the preparation of silphenylene derivatives that are non-toxic, non-allergenic, stain resistant, and with sufficient flexibility and color adaptability to be used as a technically reliable clinically acceptable extraoral maxillofacial prosthesis (i.e., artificial skin) in the facial regions of humans of different races and colors. The goal of the material development is to prepare a material which shall be: 1. Capable of being easily, reliably and inexpensively fabricated to various human facial shapes and forms and to various human racial colors and tones. 2. Applicable for clinical use and potentially acceptable to clinicans active in the area of rehabilitation. 3. Capable of withstanding the stress of environmental sunlight, temperature and humidity without deterioration to the material's flexibility and color for a nimimum of 2 years.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE42436-01
ORGANIZATION.....	UNION CARBIDE CORPORATION
ADDRESS.....	BOUND BROOK NJ
INITIAL START DATE.....	06-01-74
EXPIRATION DATE.....	05-31-75
ORGANIZATION CODE.....	EXP
PROJECT DIRECTOR.....	ROBESON, LLOYD M
NIDR PROJECT OFFICER.....	KAKEHASHI, SAMUEL
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

IMPROVED MATERIALS FOR EXTRAORAL PROTHESIS

OBJECTIVES AND WORK SCOPE:

Independently, and not as an agent of the Government, the Contractor shall exert his best efforts in the preparation of polymer derivatives that are non-toxic, non-allergenic, stain resistant, and with sufficient flexibility and color adaptability to be used as a technically reliable clinically acceptable extraoral maxillofacial prosthesis(i.e., artificial skin) in the facial regions of humans of different races and colors. The goal of the material development is to prepare a material which shall be: Capable of being easily, reliably and inexpensively fabricated to various human facial shapes and forms and to various human racial colors and tones; applicable for clinical use and potentially acceptable to clinicians active in the area of rehabilitation; and capable of withstanding the stress of environmental sunlight, temperature and humidity without deterioration to the material's flexibility and color for a minimum of 2 years.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE42437-01
ORGANIZATION.....	UNIVERSITY OF CONNECTICUT
ADDRESS.....	FARMINGTON CT
INITIAL START DATE.....	06-15-74
EXPIRATION DATE.....	06-14-75
ORGANIZATION CODE.....	EXP
PROJECT DIRECTOR.....	TANZER, JASON M
NIDR PROJECT OFFICER.....	RIZZO, ANTHONY A
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

IN VITRO SCREENING OF CHEMICALS TO PREVENT PERIO PLAQUE

OBJECTIVES AND WORK SCOPE:

The Contractor will establish an in vitro plaque forming system to test a variety of agents for their potential to: (a) prevent plaque formation; (b) prevent plaque growth; and/or (c) remove plaque. He will also determine the lowest effective concentrations of agents found active in the aforementioned tests. Five organisms, which are known to form plaque in vitro, are to be used in the test system, including Actinomyces naeslundii, A. israelii, and A. viscosus as well as two chosen by the Contractor.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE42438-01
ORGANIZATION.....	FORSYTH DENTAL CENTER
ADDRESS.....	BOSTON MA
INITIAL START DATE.....	07-01-74
EXPIRATION DATE.....	06-30-76
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	TAUBMAN, MARTIN A
NIDR PROJECT OFFICER.....	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

EFFICACY OF ANTIGENIC COMPONENTS IN ANTI CARIES VACCINES

OBJECTIVES AND WORK SCOPE:

The Contractor shall investigate the effects of specifically induced salivary antibody to enzymes, enzyme fractions or enzyme-associated fractions of Streptococcus Mutans upon plaque bacteria and dental caries in pathogtn-free and gnotobiotic rats and hamsters.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE42439-01
ORGANIZATION.....	UNIVERSITY OF CALIFORNIA
ADDRESS.....	SAN FRANCISCO CA
INITIAL START DATE.....	06-28-74
EXPIRATION DATE.....	06-27-75
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	WYCOFF, SAMUEL J
NIDR PROJECT OFFICER.....	BOWEN, WILLIAM H
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE:

EFFECT OF MOUTHRINSES CONTAINING CALCIUM GLYCERAPHOSPHATE

OBJECTIVES AND WORK SCOPE:

The contractor will conduct a research study to determine the effect of mouthrinses containing calcium glycerophosphate on the chemical composition and development of plaque in humans.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE42440-01
ORGANIZATION.....	NEW YORK STATE UNIVERSITY
ADDRESS.....	ALBANY NY
INITIAL START DATE.....	06-15-74
EXPIRATION DATE.....	06-14-75
ORGANIZATION CODE.....	EXP
PROJECT DIRECTOR.....	GENCO, ROBERT J
NIDR PROJECT OFFICER.....	RIZZO, ANTHONY A
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

IN VITRO SCREENING OF CHEMICALS TO PREVENT PERIO PLAQUE

OBJECTIVES AND WORK SCOPE:

The contractor will establish an in vitro plaque forming system to test a variety of agents for their potential to: prevent plaque formation; prevent plaque growth; and/or remove plaque. He will also determine the lowest effective concentrations of agents found active in the aforementioned tests. Five organisms, which are known to form plaque in vitro, are to be used in the test system, including Actinomyces naeslundii, A. israelii, and A. viscosus as well as two chosen by the contractor.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE42441-01
ORGANIZATION.....	UNIVERSITY OF IOWA
ADDRESS.....	IOWA CITY IA
INITIAL START DATE.....	07-01-74
EXPIRATION DATE.....	06-30-75
ORGANIZATION CODE.....	EXP
PROJECT DIRECTOR.....	MACKENZIE, IAN C
NIDR PROJECT OFFICER.....	FRAZIER, PAUL D
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

DETERMINATION ROLE NUTRITION EPITHELIUM ORAL MUCOUS

OBJECTIVES AND WORK SCOPE:

The objectives of this research project is to determine the influence of protein, calorie, and vitamin deficiencies on oral mucous membranes in experimental animal model systems. Comparisons will be made between undernourished animals and those maintained on normal diets to determine the separate effects of chronic, progressive protein, calorie and vitamin deficiency on the health of the oral tissues. Tests conducted on the oral tissues of 3-4 year old Rhesus monkeys will determine; cell turnover rates; level of keratinization in deratinizing epithelium; degree of alteration of metabolic process (enzyme systems or protein synthsis); and studies of basement membranes of the various epithelial linings.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE42442-01
ORGANIZATION.....	UNIVERSITY OF WASHINGTON
ADDRESS.....	SEATTLE WA
INITIAL START DATE.....	07-01-74
EXPIRATION DATE.....	05-31-76
ORGANIZATION CODE.....	EXP
PROJECT DIRECTOR.....	ENWONWU, CYRIL
NIDR PROJECT OFFICER.....	FRAZIER, PAUL D
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

DETERMINATION ROLE NUTRITION EPITHELIUM ORAL MUCOUS

OBJECTIVES AND WORK SCOPE:

The objective of this research project is to determine the influence of protein, calorie, and vitamin deficiencies on oral mucous membranes in experimental animal model systems. Comparisons will be made between undernourished animals and those maintained on normal diets to determine the separate effects of chronic, progressive protein, calorie and vitamin deficiency on the health of the oral tissues. Tests conducted on the oral tissues of 3-4 year old Rhesus monkeys will determine (1) cell turnover rates, (2) level of keratinization in keratinizing epithelium, (3) degree of alteration of metabolic process (enzyme systems or protein synthesis), and (4) studies of basement membranes of the various epithelial linings.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE42443-01
ORGANIZATION.....	UNIVERSITY OF MICHIGAN
ADDRESS.....	ANN ARBOR MI
INITIAL START DATE.....	06-28-74
EXPIRATION DATE.....	06-27-77
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	GRAVES, RICHARD C
NIDR PROJECT OFFICER.....	JOLY, OLGA
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

TITANIUM TETRA & ACIDULATED PHOSPHATE FLUORIDE CARIES

OBJECTIVES AND WORK SCOPE:

The proposed trial is double-blinded and involves children 11-12 years of age who shall be assigned randomly to two test groups(TiF4 and APF) and one placebo-control group. The selected study site must be stable, have a high prevalence of dental caries, have less than 0.4 ppm F in the drinking water and have a low level of dental care. The sample size will be estimated according to the increment of dental caries in that particular population, the variance, the expected magnitude of the difference, and the attrition rate. Treatments are to be given at the initiation of the study and every six months thereafter for a period of two years. DMFS clinical data will be obtained immediately prior to initiation of treatments, and at 12 and 24 month intervals.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE42444-01
ORGANIZATION.....	UNIVERSITY OF OREGON
ADDRESS.....	PORTLAND OR
INITIAL START DATE.....	06-28-74
EXPIRATION DATE.....	06-27-78
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	LU, KUO H
NIDR PROJECT OFFICER.....	HEIFETZ, STANLEY B
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

EFFECT OF SPECIFIC METHODS OF FLUORIDE ADMIN ON CONTROLLING CARIES

OBJECTIVES AND WORK SCOPE:

This is a clinical trial designed to determine whether high-level, short-term application of fluoride is more efficacious than a low-level, long-term method. A comparison will be made between five-minute applications of acidulated phosphate fluoride gel (1.23% F) in custom-fitted trays for 10 consecutive school days under dental hygienist supervision and a one-minute use of fluoride mouthrinse (0.023% F) each school day for the duration of two school years. The comparative effectiveness of these two modes of application would be determined by the dental caries experience of study subjects.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE42445-01
ORGANIZATION.....	FORSYTH DENTAL CENTER
ADDRESS.....	BOSTON MA
INITIAL START DATE.....	06-16-74
EXPIRATION DATE.....	06-15-77
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	DEPAOLA, PAUL F
NIDR PROJECT OFFICER.....	HEIFETZ, STANLEY B
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

HIGH & LOW, SHORT & LONG TERM FLUORIDE TO CONTROL CARIES

OBJECTIVES AND WORK SCOPE:

This is a clinical trial designed to determine whether high-level, short-term application of fluoride is more efficacious than a low-level, long-term method. A comparison will be made between five minute applications of acidulated phosphate fluoride gel (1.23% F) in custom-fitted trays for ten consecutive school days under dental hygienists' supervision and a one-minute use of fluoride mouthrinse (0.023% F) each school day for the duration of two school years. The comparative effectiveness of these two modes of application would be determined by the dental caries experience of study subjects.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE42446-01
ORGANIZATION.....	SOUTHERN RESEARCH INSTITUTE
ADDRESS.....	BIRMINGHAM AL
INITIAL START DATE.....	06-28-74
EXPIRATION DATE.....	06-27-75
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	COWSAR, DONALD R
NIDR PROJECT OFFICER.....	MIRTH, DALE B
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION

TITLE:

FLUORIDE RELEASING SYSTEM FOR PROLONGED ORAL USE

OBJECTIVES AND WORK SCOPE:

The objective of this research project is to develop a fluoride-containing material that: will release fluoride at a constant predetermined linear rate for a period of at least six months without maintenence or adjustment; can be easily applied or attached in the mouth (attachment to a tooth or teeth by adhesive or orthodontic bands, or as part of a space maintainer, or a simple adhesive coating); can be completely and safely removed at any time; and should contain materials that exhibit a very low order of toxicity in animals, are harmless to the teeth and harmless to and non absorbable through the oral and gastrointestinal mucosa.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE71475-10
ORGANIZATION.....	SOUTHWEST FOUNDATION RESEARCH & EDUCATION
ADDRESS.....	SAN ANTONIO TX
INITIAL START DATE.....	06-28-67
EXPIRATION DATE.....	06-30-74
ORGANIZATION CODE.....	INT
PROJECT DIRECTOR.....	REED, O M
NIDR PROJECT OFFICER.....	HAMNER, JAMES E
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

STUDY OF BETAL QUID CARCINOGENESIS

OBJECTIVES AND WORK SCOPE:

The main objective of this study is to produce carcinoma in the baboon's cheek pouch, with a secondary objective of studying the carcinogenic potential of each of the ingredients of betel quid, namely: betel leaf, areca nut, lime, and tobacco, and also to study their interplay. The baboons are divided into two groups, i.e. plain betel quid and betel quid plus tobacco. They are maintained on a protein deficient diet. Cheek pouches are created surgically, and the betel quid inserted 3 times per week. After 48 months, half of the animals in each group will be placed on normal diet, and betel quid treatment of their buccal pouches will cease. At 1,3,6,9, and 12 months biopsies will be taken to determine if these buccal pouches can return to normal when suspected carcinogen is removed. The other animals will be continued under the original regimen.

SALIENT RESULTS TO DATE:

In clinical appearance, four of the five baboons which continued to receive betel treatment for 58 months exhibited continued inflammation and ulceration in the treated cheek pouch. One animal, however, appeared with a normal pouch. The histopathological picture on the 55 month biopsy specimens demonstrated epithelial atypia on all nine baboons, whether they were on the betal quid for 55 months or off it for seven months. Usually, in the group taken off betel for seven months, the atypia was less pronounced. In two of the three baboons in the betel/tobacco group, which showed carcinoma-in-situ after 48 months of treatment, regression of the lesions had occurred after 53 months in the particular area biopsied. These results remained the same after 55 months; however, one other baboon in this group had proceeded on to carcinoma-in-situ. Neither of the two baboons in the betel quid-only group exhibited malignancy.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE71476-10
ORGANIZATION.....	SOUTHWEST FOUNDATION RESEARCH & EDUCATION
ADDRESS.....	SAN ANTONIO TX
INITIAL START DATE.....	06-27-67
EXPIRATION DATE.....	06-30-74
ORGANIZATION CODE.....	INT
PROJECT DIRECTOR.....	REED, O M
NIDR PROJECT OFFICER.....	HAMNER, JAMES E
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

REIMPLANTATION OF BABOON TEETH

OBJECTIVES AND WORK SCOPE:

The objectives of this research effort are to observe in time sequence the response of the surrounding periodontium to the implantation of ceramic, polymethylmethacrylate, prolyte carbons, titanium, and other possible artificial materials and to the heterogenous transplantation of natural teeth in adult baboons.

SALIENT RESULTS TO DATE:

The pyrolite carbon bladevents show great promise to date. In clinical tests they are quite stable over one year. Microscopically, they appear extremely biocompatible. Both the Titanium bladevents and Vitalium anchor implants exhibit stability and good tissue adaptation to date; however, our longest term implants in these two categories are six months. With more histologic specimens harvested from the periodontal ceramic graft study, we can determine the fate of the calcium aluminate, its ability to enhance alveolar bone growth into the osseous defect area, its usefulness as a matrix for new bone, and its biocompatibility in this anatomical site. Also, with certain two and three year allograft block specimens proposed to be removed in April, 1973, the tooth rejection phenomenon with the allograft in place will be studied.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER.....	N01 DE81262-07
ORGANIZATION.....	THE KENDALL COMPANY
ADDRESS.....	BARRINGTON IL
INITIAL START DATE.....	06-28-68
EXPIRATION DATE.....	10-31-73
ORGANIZATION CODE.....	NCP
PROJECT DIRECTOR.....	MELLBERG, JAMES R
NIDR PROJECT OFFICER.....	ENGLANDER, HAROLD R
NIDR CONTRACT SPECIALIST.....	KEEFER, DAVID

TITLE:

MICROCHEMICAL ANALYSIS TOOTH FLUORIDE UPTAKE IN ENAMEL

OBJECTIVES AND WORK SCOPE:

The contractor will perform a microchemical analysis of the fluoride uptake in tooth enamel. Specifically, the contractor will: Remove thin layers of tooth enamel by immersion in perchloric acid by the method of Ohmori, Brudevold, and Gron; Conduct fluoride determinations for each of the tooth layers removed; Conduct experiments to determine whether artifically acquired enamel fluoride can be washed out in artificial saliva; and Perform fluoride and calcium assays on tooth enamel specimens supplied by the Project Officer.

SALIENT RESULTS TO DATE:

Progress has been very satisfactory, and over 15,000 Fluoride (F) analyses have been performed. The Contractor has produced useful enamel F data from the NIDR Clinical studies in Stickney, Illinois, and has demonstrated that initially high concentrations of F are acquired by the enamel of deciduous and permanent teeth from a short series of intensive F toplications. The F slowly leeches out of the enamel for about eight months but remains significantly higher than the controls. There has been research resulting in refinement and improvement of the abrasive biopsy technic. Kendall has conducted hundreds of biopsies for the U.S. Health and Nutrition Survey, and F analysis from teeth and biopsies in the Kentucky mouth-rinse study, the NIDR clinical trial in Puerto Rico, and other NIDR studies in Stickney, Illinois, and on hundreds of rat teeth supplied by the NIDR. The Contractor has also performed miscellaneous tooth and water analyses for the NIDR and other study groups.

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